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EFFECTS OF PHLEBOTOMY ON CARDIOPULMONARY PARAMETERS AT REST AND EXERCISE WITH A COMPARISON OF CARDIAC OUTPUTS USING CO_2 AND DYE CURVES

by

JOHN N. PRIMROSE

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Effects of Phlebotomy on Cardiopulmonary Parameters at Rest and Exercise with a Comparison of Cardiac Outputs Using CO_2 and Dye Curves," submitted by John N. Primrose in partial fulfillment of the requirements for the degree of Master of Science (Physical Education).

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ABSTRACT

This thesis was designed to investigate the effects of a 10 ml/kg body weight phlebotomy upon the oxygen uptake and cardiac output at rest, submaximal exercise and maximal exercise, at the identical worklevels, directly after phlebotomy and again five days later. A subsidiary investigation compared cardiac outputs determined by dye dilution curves and carbon dioxide rebreathing methods (Campbell procedure).

Seven healthy male subjects comprised the experimental group. Preliminary studies were carried out in order to plot a graph of oxygen uptake and worklevel for each subject and also to determine the worklevel required to elicit a maximal oxygen uptake.

In order to investigate cardiac output and oxygen uptake, quantitative measurements were made of the following parameters: arterial oxygen content, arterial-venous oxygen difference, hemoglobin concentrations, arterial pressures, total peripheral resistance, heart rate stroke volume, blood volume, central blood volume, lactates and blood viscosities.

Oxygen uptake values showed no significant decrease on the day of the phlebotomy, or five days later, in the state of standing rest, submaximal exercise or maximal exercise. Cardiac output calculated with dye dilution curves was reduced after phlebotomy 10% at rest, 17% at submaximal work and 18% at maximal worklevels. The five days post phlebotomy mean cardiac output (Campbell Method) was significantly increased 11% at the maximal exercise level above that of the pre phlebotomy cardiac output. Resting and submaximal values were unchanged.

The correlation coefficient for all paired values of cardiac outputs (CO_2 Campbell v.s. dye dilution curves) was .95 with 96% of all the comparisons falling within $\pm$ 20% of the line of identity.

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Introduction

The effects of phlebotomy on cardiopulmonary parameters has been studied quite extensively at rest but under exercise conditions the literature is sparce. None of the studies previously published have attempted to comprehensively measure the determining factors of oxygen uptake or cardiac output at exercise levels. Most of the previous studies agree that, except for motivational interference performance should be decreased after phlebotomy. The decrease in performance was minimal in "sprint" type activities, and more pronounced in endurance exercises. The performance decreases were relative to the amount of blood lost.

Oxygen uptake values, at a constant worklevel on a bicycle ergometer, have not been studied under exercise conditions in the post phlebotomy state, nor has cardiac output been investigated. By careful measurement of the parameters that determine the oxygen carriage system and cardiac output, we should be able to account for any physiological adjustments made after phlebotomy.

Cardiac output determination with CO_2 rebreathing methods has not been studied after a blood loss. We wanted to examine the Campbell method[43] and see if our results coincided with their findings in regards to comparisons made with dye curves and the reproducibility of the method.

Delimitations

1. The study was limited to seven healthy male subjects.
2. There was no attempt made to randomly select the subjects. All were volunteers including the author.

Limitations

1. The results are limited by possible human errors by the author and the attending technicians.
2. The results are limited by possible errors in the testing equipment and analysis techniques.

REVIEW OF THE LITERATURE

This investigation examines the effects of phlebotomy (10 mls./ kg. of body weight) on different parameters affecting cardio-respiratory fitness; this may be defined as "An ability to maintain the processes of metabolic exchange as close to the resting state as is mutually possible during performance of a strenuous and fully learnt task for moderate time, with a capacity to reach a higher rate of working than the "unfit" and to restore promptly all equilibria which are disturbed". (66) These determinants of "cardio-respiratory fitness" make reference to the optimum relative values of the processes involved in metabolic exchanges, and these relationships to the potential capacities of the different processes of metabolic exchange. The maximal oxygen uptake is the highest amount of oxygen uptake that the individual can attain during physical work and is the most commonly measured component of cardio-respiratory fitness. The maximal oxygen uptake is a measure of the maximal energy output by aerobic processes, and the functional capacity of the circulation; since there is a high correlation between the maximal cardiac output and the maximal aerobic power.

Different researchers(5, 16, 18, 42)have studied the effects of phlebotomy of 500 mls. of blood on the physical work capacity by measuring oxygen uptake values and work performance times.

Observations by Karpovich and Millman(45) on college athletes giving 500 mls. blood led to the conclusion that in exercises of speed, performed once a day lasting about a minute and depending on oxygen debt, performance may not be adversely affected. However, in exercise depending upon endurance, the performance was decreased, and two or three weeks elapsed before the subjects returned to normal. The return to normal performance was thought to be dependant upon the hemoglobin regeneration. Two of their subjects, a sprinter and short distance swimmer, equalled their pre phlebotomy records within hours of the blood loss and their performance was attributed to the frantic motivational effort to prove that blood loss would not affect their performance.

Spealman, Bixby, Wiley and Newton (69) tested the ability of young men to perform bicycle ergometer tests in a warm environment (33°C) , after a phlebotomy of 500 mls. They also found an immediate and significant decrease in the ability to exercise for 20 minutes on a bicycle ergometer within two hours of the phlebotomy. With an infusion of human serum albumin, corresponding to the amount of blood lost, performance was equalled on the ergometer. Pulse rate was significantly increased during exercise after the phlebotomy. Hemoglobin concentration was reduced following phlebotomy and albumin infusion. The levels of blood volume appeared to affect the performances rather closely whereas no consistent relationship between hemoglobin concentration and performance was found. With a normal blood volume restored by serum albumin infusion the exercise performances were not decreased even though the hemoglobin content was lower.

Balke, Grillo, Konecci and Luft (5) phlebotomized fourteen subjects a total of 500 mls. and investigated work capacity on a treadmill by increasing the slope 1/2% per minute with a constant speed of 3.5 m.p.h. Subjects were tested one hour, two or three days later, and again eight to ten days later. The average duration of the test, which had a cut-off point about 187 beats per minute, was considerably less in the post phlebotomy state (1 hour), equal (after two or three days) and longer (after eight to ten days). The pulse rate average at higher work loads was increased about 6 beats per minute during heavy exercise one hour after phlebotomy but eight to ten days later the pulse rate was lower for the equivalent work levels. Maximal oxygen uptake was not achieved one hour after phlebotomy (9% decrease) but this could be due to termination of the test before the heart rate reached 190 beats per minute. Two days later the MVO_2 was still not reached but ten days later an increase of 5% was recorded for the MVO_2. Mean arterial blood pressure was reduced in all post phlebotomy tests as was hemoglobin concentration.

Dennison(10) divided twenty young athletes into a control and experimental group in which only the experimental group gave blood. The control group received needles in their arms but no blood was drawn. The test item consisted of making as many pedal revolutions as possible in two minutes on a bicycle ergometer with a fixed resistance of fourteen kilograms. All subjects were retested two hours, twenty-four hours and seven days after phlebotomy. Both the experimental and control group showed a significant increase in performance on all post phlebotomy tests. These findings suggest that

a 500 ml. phlebotomy does not cause a decrease in performance in "sprint type"events. Their findings of no significant differences may indicate; a training effect was present, an increase in cycling efficiency or a strong desire of the subjects to prove that the phlebotomy would not decrease their performance.

Howell and Coupe(42) equated twelve subjects into two equal groups based on treadmill performance time. All subjects believed they had given blood, but only the experimental was really bled. The treadmill test was repeated immediately after blood loss, 24 hours, and seven days later. Immediately following blood donation there was a mean decrease in performance times, then an increase was found in both the 24 hour and post seven day test. The control group displayed a similar trend as did the experimental group indicating that motivational factors influenced the results. No significant differences were found between groups. No significant differences were found in exercise heartrates.

Brown (9) investigated the maximal oxygen uptake, maximal oxygen pulse and maximal heartrate on a treadmill, four days, eight days and twelve days after a 500 ml. phlebotomy. Maximal oxygen uptake values did not differ significantly from the control values on any of the post phlebotomy test (day 4, 8 or 12), however, the day 4 values and day 8 values were significantly less than the day 12 values. Oxygen pulse values followed a similar trend. Maximal heart rates did not show a significant difference between any of the test days.

The present investigation involving a main phlebotomy of 10 ml./kg. of body weight plus a conommitant blood loss of 4 ml./kg. for blood samples and cardiac outputs results in hypovolemia leading to mild experimental hemorrhagic shock. The mental trauma of an unexpected injury is most mostly absent. Circulatory shock is an abnormal state of the circulation whereby the cardiac output is reduced so that the tussues of the body may be damaged because of the lack of adequate tissue blood flow. We are dealing with nonprogessive shock in which the cardiac output is not reduced enough to cause weakening of the heart musculature, walls of blood vessels or the vasomotor center. Either a decrease in the ability of the heart to pump blood or a decrease in the venous return may lead to a decrease in the cardiac output. Generally, decreased cardiac output causes a decrease in the arterial pressue and thus a decrease in systemic blood flow unless compliance of the arterial and venous capacitance vessels is decreased. Decreased nutrition of the tissues may lead to a decrease of vasomotor activity and tissue ischemia. Without strong sympathetic response via the pressoreceptor reflexes and the central nervous systen on ischemic response and increase in capillary permeability and vascular dilatation may occur which may further lead to a decrease in the blood volume and venous return supported by cardiac depression.

An increase in the VO_2 that occurs in moderate hemorrhage in dogs could be due to the stimulation of the sympathoadrenal system and catecholamine release which would produce an accelerated turnover of free fatty acids, (59). If acidosis is present the calorigenic effect of the catecholamines is neutralized. If hypovolemic shock is severe,

following a massive hemorrhage, there will be a decrease in oxygen consumption which can be accounted for by the marked decrease in the oxygen transport capacity of the circulating blood, (64) Hypotension is known to stimulate the sympathoadrenal system which leads to an increase in catecholamine release thus the increase in oxygen uptake. Circulatory and metabolic changes e.g., rise in blood pressure, heart rate and blood flow, are accompanied by higher energy requirements,(59) An accelerated breakdown of the triglycerides and an increased turnover rate of the released F.F.A. and resynthesis of triglycerides have been postulated as the mechanisms of the calorigenic effect of catecholamines, (59.) An increased oxygen uptake in the presence of a decrease in oxygen transport is not likely since acidosis decreases the catecholamine calorigenic effects,(36) Halmagyi and Kennedy in studying hypovolemic dogs concluded that the O_2 extraction ratio in shock was shown to be determined by O_2 transport, blood pressure, and blood temperature and that in hypovolemia there was a more effieient O_2 exchange between blood and tissues. Furthermore, a fall in the transmural pressure in the pre-capillary sphincter region produces pre capillary sphincter relaxation enlarging the functional capillary surface area and allowing for improved O_2 extraction in the face of reduced blood flow.

The available oxygen, which is flow limited, - equals the product of cardiac output and oxygen content, oxygen content being determined by the hemoglobin concentration and arterial oxygen saturation. Oxygen consumption usually rises above rest levels after hemorrhage as a result of increased ventilatory work and sympathetic activity. Diminishing cardiac output contributes to the reduction of arterial oxygen transport.

Cardiac output distribution changes during the transition from rest to exercise. The working muscles may increase their blood flow to 50 times the resting amount, (10.) Blood flow to the heart is increased and blood flow to the skin is increased to dissipate heat although at maximal exercise the skin, surrenders most of its blood to the working muscles. The kidney and abdomen blood flow is reduced in exercise while the brain blood remains fairly constant.

In hemorrahagic shock at rest regional blood flow to the mesenteric hepatic, renal and ileofemoral arteries is disproportionately decreased. Flow in these vessels is apparently reduced in favor of maintaining circulation to the carotid, coronary, and hepatic arteries,(67.) No information is available on redistribution or cardiac output after hemorrhage under exercise conditions. In resting man blood loses of 460 - 900 mls. caused a decrease in central blood volume, and the per cent decrease approximately equalled that of the total blood volume, (31.)

Saltin (65) studies three subjects after dehydration reduced plasma volume up to 25%. After dehydration, the major change in the hemodynamic response to submaximal work in a sitting position was a decrease in stroke volume and an associated increase in heart rate; the cardiac out remained about the same. Dehydration produced no significant change in oxygen uptake, cardiac output or stroke volume during maximal exercise in a sitting position, although the maximal work time was much shorter,(65.) Blood lactate was also reduced.

Ekelund, (18), studied the effects of exercise and posture on blood volume. They found a decrease in plasma volume upon a change of posture from supine to sitting and also shortly after starting exercise both in supine and sitting positions. These changes were reflected in an increase of total body hematocrit in exercise. Assuming changes in total blood volume Holmgren, (39), estimated the decrease in blood volume during exercise and found a decrease after five minutes of exercise which, after 15 minutes of exercise, amounted to seven per cent of the resting values. Ekelund also found a 9.3% blood volume decrease after ten minutes of exercise, caused by a 14.3% decrease in plasma volume. However, during exercise between 10 and 15 minutes, there were no significant changes in blood volume or plasma volume. Therefore, the change in bolld volume due to a decrease of plasma volume is predominantly at the start of exercise. The exchange of water, between the circulating blood and spaces outside is dependent upon the hydrostatic pressure and effective osmotic pressure of the blood inside the capillaries and the tissues surrounding the capillaries. As blood flow increases in the muscles during exercise the precapillary sphincters release and furthermore, the hydrostatic pressure in the capillaries is increased by virtue of the relaxation of the resistance vessels. There is a net movement of water and solutes into the muscle tissue. This accounts for the decrease in circulation blood volume at the start of exercise. Lymph flow is increased during exercise by the massaging effects of the muscles, but this increase is not sufficient to maintain blood volume which is also decreased by the loss of water through perspiration and the respiratory system.

Adamson and Hillman, 1, studied these blood volume changes along with plasma protein replacement after blood loss. No significant influx of salt and water was observed and the plasma protein concentration remained constant after a 15% to 20% phlebotomy. It appeared that the plasma proteins replaced in the circulation after phlebotomy originated from some pre-existing extravascular pool. Furthermore, their findings show that the hematocrit value is a poor indicator of blood volume decrease after a phlebotomy. Blood letting usually occurs in a prone position and upon standing up there is a decrease in the plasma volume regardless of blood loss. There is no sudden increase in protein production.

The sympathetic system is activated after phlebotomy and controls the arterial pressure with the decreasing blood volume. When arterial pressure is decreased and pluse pressure narrowed there is a reduction of afferent impulses from the baroreceptors in the carotid sinus and aortic arch, (11), resulting in the activation of the sympathetics efferents to the heart and blood vessels. Furthermore, after hemorrhage the increase in sympathetic discharges from the medullary cardiovascular center aids in a reduction in chemoreceptor blood flow.

Hemorrhage may cause emotional excitment and activation of the cortico-hypothalamic vasomotor neurons, which usually reinforces the sympathetic adrenergic discharge but sometimes excitation of the sympathetic cholinergic vasodilator response, the dilation of the arteriovenous anastomoses in the skeletal muscle causes a sudden decrease in the fraction of the cardiac output perfusing the brain and fainting results, (11). (vasovagal reaction).

Activation of the sympathetic system results in liberation of norepinephrine from the postganglionic nerve ending and release of norepinephrine and epinephrine from the adrenal medula, (21). The locals levels probably control the cardiovascular system rather than the amount released by the medulla.

Both the heartrate and myocardial contractility were increased in an effort to maintain cardiac output. Total peripheral resistance TPR may not change as flow and pressure are decreased. The release of vasodilator materials from ischemic organs, or local accumulation of metabolites may cause vasodilation, (63). Blood vessels in different regions respond differently to catecholamines and regional resistance are different.

Physiological dead space is increased after phelbotomy due to the (26) underperfusion of well ventilated alveoli.

Coronary and cerebral blow flow is not decreased after mild phlebotomy because "selective vasoconstriction" maintains the arterial pressure in these vital organs.

The veins contain about two-thirds of the total blood volume and their capacity is extremely variable. The state of sympathetic discharge results in constriction of the capacitance and resistance vessels, however, in the resistance vessels the resistance is more marked in the precapillary than postcapillary segment which aids hemodilution.

The body responds to phlebotomy by increasing the rate of erythropoiesis, (14, 37, 51). Hamstra and Block, (37), found that hemoglobin production was most likely to be limited by inadequate availability of iron to erythropoiesis. Reticulocyte release was also found increased. The intensity of the stimulus for erythropoiesis is inversely proportional to the hematocrit level, (14). The hemopoietic rate was increased one and one-half times normal after a phlebotomy of 500 ml. The variability from two or three weeks to three months in recovery from a 500 ml. phlebotomy may be explained on the basis of variable iron stores, (14).

Blood viscosity is primarily dependent upon the concentration of red blood cells in the plasma. Increasing the hematocrit causes a marked increase in peripheral vascular resistance and decrease in peripheral blood flow, (44). An increased cardiac output in acute experimental anemia depends more upon a decreased blood viscosity than upon a reduction in either O_2 capacity or $\bar{P}v_{O2}$,58.

Sproule, Mitchell and Miller, (70), examined cardiopulmonary responses to exercise in patients with anemia and found at rest an expansion of hemodynamic compensatory mechanisms could handle the delivery of oxygen by increasing the ventilation, cardiac output, a shift to the right of the oxygen dissociation curve, and an increased desaturation of venous blood which because of the Haldane effect, augmented carbon dioxide carriage. At heavy exercise these adjustments were insufficient to carry the required oxygen amount needed. Systemic oxygen transport was maximum at normal hematocrits (29) and decreased in anemic dogs. Viscosity changes in anemia may partly offset a reduced oxygen transport, by augmenting an increased cardiac output.

Butler, (9), has reviewed experimental evidence for the validity of CO_2 rebreathing methods in the determination of cardiac output. Various authors have compared CO_2 rebreathing cardiac outputs with Fick methods, (45), (55), dye dilution curves, (23), (43), and acetylene, (47). Estimates of veno-arterial differences in CO_2 content and of cardiac output using the rebreathing method were compared with those using indicator dilution at work loads from 300 to 900 kmp./min. and the results were satisfactory, (43). The reproducibility of the CO_2 method was good, (23), and a correlation of .87 was found between cardiac output values determined by the CO_2 and dye dilution methods at maximal exercise on a bicycle ergometer.

METHODS AND PROCEDURES

The investigation was divided into four sections. A preliminary study was conducted on the seven subjects in order to estimate the worklevels required to elicit 70% of the maximum oxygen uptake (MVO_2) and determination of the actual MVO_2. These results formed the basis for appropriate worklevels to be used in the pre, post and five day post phlebotomy investigations.

Seven healthy male volunteer subjects ranging in age from 21 to 51 were selected for this study.

The subjects were requested to refrain from exercise and smoking before the tests. Fluid intake was controlled and the laboratory temperature remained at $73 \pm 2°F$.

Preliminary Studies

Preliminary studies on seven subjects were carried out to determine the oxygen uptake (VO_2) at rest and various worklevels terminating in an MVO_2 level. All subjects reported for four testing sessions, generally with a day of rest separating each test. Each test consisted of the VO_2 being determined at rest and four worklevels of increasing intensity with the final workload being in the maximal VO_2 range.

Testing was conducted by first collecting a two minute expired gas sample with the subject in an upright position. The worklevels selected for the day approximated 40%, 60%, 80% and 100% of the estimated MVO_2. A five minute warmup on the bicycle ergometer preceded a five minute ride at the appropriate worklevel. Ten minute rest periods separated the rides. During the preliminary tests a total of 12 to 16 comparisons of exercise VO_2 were plotted in a graph. For all subjects a linear relationship was found in the submaximal range which levelled into a plateau at maximal worklevels (figure 1).

Determination of numerous VO_2 spread over four testing sessions will give a true estimate of the VO_2 versus worklevel relationship and provide the subject with the opportunity to familiarize himself with the testing procedure.

The submaximal worklevel, for pre and post phlebotomy test, was selected as the level consuming $70 \pm 5\%$ of the measured MVO_2. The MVO_2 plateau occurred when the VO_2 failed to rise by more than 100 mls. of oxygen per 100 kilogram meters per minute of work. The lowest worklevel eliciting MVO_2 was observed on the graph at the initial point of the plateau (figure 1). Selection of this worklevel was influenced by the ability of the subject to ride for five and one half minutes since it was anticipated this time might be required to complete all the pre and post phlebotomy measurements.

Pre Phlebotomy Investigation

Subjects reported to the hospital in the morning where arterial and venous catheterization was performed under standard sterile conditions. After a local anaesthetic, an 0.034" teflon catheter was introduced into the right brachial artery by the percutaneous Seldinger technique and positioned in the subclavian artery. Next, a 6 French Raycatheter (external diameter 2 mm) was introduced using a cut-down procedure into the right anticubital vein and placed in the superior vena cava. Fluroscopy confirmed the position of both catheters.

The subject then reported to the laboratory in the Clinical Sciences Building. Circulatory and respiratory measurements were taken at rest and at worklevels corresponding to the 70% MVO_2 and MVO_2 itself using the following procedure. The arterial catheter was connected to a Statham P 2 3 D 6 pressure transducer, via a 3-way double stopcock (Dich) which was positioned level with the subclavian artery. A bottle of sterile normal saline (Cutter) was attached to the stopcock system to be used for flushing the catheter and syringe. The venous catheter (80 cm.) was connected to a 2 u Cornwall spring syringe to be used to inject Indocyanine (cardio-green from Hynson, Westcott and Dunning Inc. Baltimore) for cardiac output dye curves. The arterial catheter was frequently flushed to prevent clotting with heparinized saline. The venous catheter contained cardio-green.

Electrocardiogram leads were attached with a Sanborn cable in the following manner; L.A. lead over the apex of the heart, R.A. lead on the lower right side of the chest wall, and the R.L. lead over the apex of the right scapula.

The subject was then fitted with a head harness, supporting a 2 way Godart stopcock (1" diameter) and large Collins mouthpiece (with very little airway resistance) fitted into a Collins Triple "J" high velocity valve containing 180 cc. of dead space (figure 2). With this valve, inspiratory resistances are almost immeasurable at flow rates below 100 l./min. Corrugated plastic reinforced tubing (1 1/2" diameter) connected the valves to 150 liter Douglas bags.

Calibration of the gas analysis equipment was done at different intervals with gas guaranteed to $\pm$ 0.05% of the specified concentration. A Quinton Uniwork Bicycle Ergometer (Model 844) of the constant work load type was employed with work load increments of 100 kilogram meters per minute. This bike was calibrated at the factory to a sensitivity of 2 K.G.M.

Resting Measurements

The subjects stood quietly while straddling the ergometer during a two minute collection of expired gas. For all rest and exercise samples the valves were opened and closed at the end of an expiration. The Douglas bags were shaken before gas analysis.

Expired air for gas analysis was drawn through a Godart Capnograph and then forced through a Beckman E 2 oxygen analyzer. Measurements of the oxygen content was done a "0" flow rate. Expired air was blown through a Parkinson - Cowan volumeter by a Collins motor blower. The volumeter was previously calibrated by a Collin chain supported 120 liter gasometer.

Heart rate and arterial blood pressure were recorded on an 8 - channel Beckman Type R Dynograph.

Cardiac output dye curves were recorded on the Beckman Dynograph. The Cornwall syringe was used to inject cardio-green (conc. of 3.33 mg./ml and val. of 1.8 mls. determined by weight on a Sartorius Scale) into the vein. A Harvard infusion-withdrawal rate of 14.8 mls./minute, pulled blood through a Waters XP 30 2 Densitometer. No blood was reinfused. A gilford Dye-Curve Computer (Model 104) and Mean Transit Time Computer (Model 104-A) recorded values from the densitometer. Two acceptable dye curves were recorded at rest and each exercise level. During each investigation dye curves were calibrated by adding known quantities of dye to aliquots of blood which were drawn through the densitometer.

Later, calculation of the area under the dye curves was performed using the Woods formula (79). The Steward-Hamilton technique was applied for semilogrithmic extrapolation of the downslope curve which was necessary for determination of true mean transit time and

subsequently central blood volume.

Immediately following the withdrawal of about 10 mls. of blood for acrdiac outputs, another 10 mls. were drawn for estimation of blood gases, viscosities and hemoglobin concentrations. An Instrumentation Laboratories $pH/PCO_2/PO_2$ Electrometer (Model 113) was employed to measure blood gases. Oxygen saturation, hemoglobin and per cent carboxyhemoglobin were determined on an I.L. Co-oximater (Model 182). Duplicate blood samples (about 3 mls. were added to a pair of cold centrifuge tubes each containing 5 mls. of trichloroacetic acid. Lactic acid was analyzed with the Enzymatic method of Ellis, Cain and Williams (23) and the absorption performed on a Unicam Ultraviolet Spectrophotometer.

Cardiac output using the CO_2 rebreathing method following Campbell's method, (43), which makes use of the Fick equation with CO_2 values;

$Q + VCO_2/C\bar{v}_{co2} - Ca_{co2}$ where Q = cardiac output in liters per mls.

$VCO_2 = CO_2$ output in mls. per min. STPD, $C\bar{v}_{co2}$ = mls. of CO_2/liter of mixed venous blood, and Ca_{co2} = mls. of CO_2/ liter of arterial blood. The VCO_2 may be measured at STP rather than STPD which gave an increased volume; but proportionally small CO_2%. Inspired air volume was measured rather than expired air. The two volumes vary slightly depending upon the respiratory quotient and any error was within $\pm$ 1%.

The inspired air volume which was traced on the Beckman dynograph was measured by a rotating heliport (Beckman potentiometer) situated on the needle axis of the Parkinson gasometer. Mean CO_2 concentration was recorded from the expired air flow through a mixing box. The readout from the CO_2 capnograph was recorded on the Beckman.

The $C\bar{v}_{co2}$ was determined by rebreathing various mixtures of CO_2 in O_2 from 5 liter rubber bags attached to the breathing mask by the Godart stopcock until one mixture produced an equilibrium pattern. The stopcock was turned at the end of a normal expiration and deep rapid rebreathing of the bag contents proceeded for 10 seconds (rate 50/min.). Gas flowing between the bag and lung system was continually monitored for CO_2 content at a flow rate of 1l./min. This equilibrium pattern was assumed when the PCO_2 values were within $\pm$ 1 mm. Hg. on an inspiration followed by an expiration. Equilibrium patterns traced on the Beckman from the CO_2 capnograph required completion before recirculation raised the $C\bar{v}_{co2}$. Where a second bag was required, 20 seconds were allowed to expel the exogenous carbon dioxide. Due to the high O_2 concentrations in the rebreathing bag all blood CO_2 tensions were converted to CO_2 contents using the standard CO_2 dissociation curve of oxygenated blood.

Campbell's connection factor $(1.4 + 2.6\ (V\dot{C}O_2$ mls./min.) was subtracted from the $P\bar{v}_{co2}$ before conversion to the $C\bar{v}_{co2}$. This connection factor accounts for the alinearity of the CO_2 dissociation curve as worklevel increases (thus $P\bar{v}_{co2}$ increases) and allows the

equilibrium rebreathing PCO_2 to be corrected so that standard CO_2 dissociation curves may be used to estimate the veno-arterial CO_2 content difference. The blood CO_2 pressure to content difference factor of 4.7 mls. CO_2/ liter whole blood was used to convert the $\bar{P}v_{co2} - Pa_{co2}$ difference to mls./l. difference in whole blood.

Arterial CO_2 content was determined from end tidal air sampled from the mouthpiece, moments before the stopcock was turned for CO_2 bag rebreathing. End alveolar air tended to give a higher Ca_{co2} thus causing cardiac outputs to be high. Whipp and Wasserman (76) calculated a correction factor that could be added or subtracted to the Pa_{co2} of end tidal air to account for the differences between the PA_{co2} and Pa_{co2}, that occur as one moves from a resting to an exercise state. The unequal ventilation-perfusion ratio at rest and increased deliverance of CO_2 during exercise determine this correction factor.

Exercise Measurements

Upon completion of the resting measurements the subject mounted the bicycle and pedalled for five minutes at a warmup level of 35% of the MVO_2. One minute of rest was then allowed during which all the instrumentation was given a final check. A six minute ride ensued at the predetermined worklevel that should evoke a 70% of MVO_2 response. After 3:30 minutes into the ride, the first dye cardiac output was inscribed followed by a second output within one minute. Blood samples for blood gases, viscosity and hemoglobin

were collected for 30 seconds starting at the fourth minute. After expired air collection, inspired air volume, mean CO_2%, end tidal and end alvedar samples were inscribed on the Beckman. Then, bags containing the CO_2 mixtures were rapidly attached to the Godart stopcock and rebreathing proceeded as described previously. Repeat bags were given 20 seconds later if necessary. The subject then rested for 15 minutes.

Maximal exercise was preceded by five minutes of warmup at 35% of MVO_2 level followed by one minute of rest. The identical sequence of tests was followed from the submaximal level but all the measurements started 30 seconds earlier to ensure completion within the five minute pedalling period, i.e., first cardiac output at three minutes. The dye cardiac outputs preceded the CO_2-cardiac outputs in most cases except where a comparison was made to check if rebreathing CO_2 had any effect on the dye cardiac outputs. In these cases, dye was injected within five seconds after the start of CO_2 bag rebreathing.

After maximal exercise, the catheters were uncoupled from the stopcocks with the commencement of a rest period lasting 45 minutes.

Total blood volume was indirectly calculated by tagging human plasma albumin with radioactive I^{131} (RISA) and also measuring the arterial hematocrit. After 10 minutes of the above resting period a six ml. blood sample was taken for a background count of any

present radiation, followed by the injection of 1 ml. (10 u c./ml. I^{131}, half-life 8 days). Ten minutes later a six ml. blood sample was taken from the opposite arm.

Following their rest a phlebotomy of 10 ml./kg. of body weight was performed from an antecubital vein over a 30 minute period. Previously, about 150 $\pm$ 20 ml. had been removed for cardiac outputs and blood samples and this loss was repeated in the post phlebotomy tests, which totalled about 4 ml./kg. Subjects were allowed to injest 250 to 300 ml. of milk or juice to replenish the fluid lost from exercise and to provide some energy.

After phlebotomy the subjects rested and then walked around for 30 minutes to allow the cardiovascular system to adjust to the phlebotomy before post phlebotomy testing.

Post phlebotomy tests duplicated the pre phlebotomy procedures. The catheters were removed at the end and the subjects remained under observation for an hour.

Five Days Post Phlebotomy Test

Five days later VO_2 values and CO_2- cardiac output determinations were performed at rest, submaximal and maximal exercise levels.

Conventional statistical techniques for small samples were applied; namely, pre and post means, standard deviation of the

means and the P value for significance of differences between means.

The P values were described as follows for the respective N - 1 degrees of freedom.

a) N.S. for p values greater than 0.05

b) * for p values between 0.05 and 0.01

c) ** for p values between 0.01 and 0.001

d) *** for p values greater than 0.001

Correlation coefficients and regression equations were calculated to compare cardiac output measurements using CO_2 and dye respectively.

RESULTS

Table I presents the physical characteristics of the subjects, maximum worklevels, oxygen uptakes and heartrates. The mean age was 29 but if subject R.T. was excluded the mean would only be 25.6 years. The mean maximal worklevel of 1414 kilogram meters per minute elicited a mean oxygen uptake of 3.23 liters per minute. The mean submaximal worklevel was 1028 kilogram meters per minute which is 72.7% of the maximal worklevel. The mean post phlebotomy maximal heart rate was 187 beats per minute which indicates the subjects were maximally taxed.

The body surface area was estimated from the Du Bois Body Surface Area Chart based on the following formula

$$(B.S.A. = \text{Weight}^{0.425} \times \text{Height}^{0.725} \times 0.007184)$$

The subjects were either ectomorphic or mesomorphic in body somatotype.

The total phlebotomy (table I I) is divided into component parts. Pre and post blood samples were required for cardiac outputs, blood gases, lactates, viscosities, hemoglobins and I^{131} blood volumes. These samples, added to the main phlebotomy of 10 ml./kg. of body weight increased the blood loss up to about 14 ml./kg. of body weight although they were spread over a total four hour period.

Table III compares the oxygen uptakes and maximal worklevels in the preliminary studies. Many of the worklevels reached in the preliminary studies were too fatiguing to be endured for a full five minutes and so the lowest worklevel eliciting a MVO_2 response was selected for the main study (figure 4).

Table IV contains all the cardiopulmonary data from the pre phlebotomy tests and table V contains the respective data from the post phlebotomy tests.

Table VI summarizes the $\dot{V}O_2$ values and cardiac outputs (Campbell CO_2 Method) from the pre phlebotomy and 5 days post phlebotomy investigations.

Oxygen Uptake ($\dot{V}O_2$ and $M\dot{V}O_2$)

There was no significant change in the mean $\dot{V}O_2$ in l./min. or in mls./kg./min. at any of states; rest, 70% $M\dot{V}O_2$ or $M\dot{V}O_2$ between the pre and post phlebotomy investigations (table VIIa and VIIb). As expected the $\dot{V}O_2$ and worklevel comparison produced a linear relationship at all levels of exercise in both the pre and post phlebotomy results. Likewise the $\dot{V}O_2$ values in liters/minute between pre and post phlebotomy and 5 days post phlebotomy were not different at the corresponding worklevels (table VIIc). Oxygen uptake (mls./kg./min.) was increased 5% at submaximal work.

Cardiac Output (C.O.)

The cardiac output calculated with dye dilution curves was reduced after phlebotomy 10% at rest, 17% at submaximal work and 18% at maximal work levels (table VIIIa and Figure 6). The 5 days post phlebotomy mean cardiac output (Campbell method) was significantly increased 11% at the maximal exercise level above that of the pre phlebotomy cardiac output. Resting and submaximal values were similar (table VIIIb).

The correlation coefficient for all paired values of cardiac outputs (CO_2 Campbell v.s. dye dilution) was 0.95 and 96% of the comparisons fell within $\pm$ 20% of the line of identity (Figure 11). Dye dilution values were 2% higher. No significant difference was found between the cardiac output means (Campbell CO_2 method and Campbell method with the Wasserman factor) although the Campbell CO_2 method gave a 5% higher mean (table VIIId). Figure 7 depicts the cardiac output reaching a plateau between the 70% $\dot{V}O_2$ worklevel and maximal worklevel in pre and post conditions.

Blood Gases (PO_2, PCO_2), pH and Volume Expired $\dot{V}E$

No significant differences in arterial PO_2, PCO_2 and pH were recorded (Table IVa and Va) although in some subjects the $\dot{V}E$ was increased in post phlebotomy testing (table XIIc). This increase in the $\dot{V}E$ was reflected in a lower PCO_2 and higher pH. There appeared in some subjects an increased VCO_2 and R.Q. after phlebotomy. The R.Q. was increased significantly only in post phlebotomy submaximal work (table XIIIb). Oxygen saturation was similar in pre and post phlebotomy tests.

Blood Oxygen Parameters

Arterial oxygen content was significantly reduced after phlebotomy; 4% at rest, 6% at submaximal exercise and 5% at maximal exercise (table IXa). Arterial-venous oxygen difference after phlebotomy was increased 29% at rest, 20% at submaximal exercise, and 12% at maximal exercise (table IXb). The arterial-venous oxygen difference is a function of the cardiac output providing the $\dot{V}O_2$ remains constant.

After phlebotomy the arterial oxygen content was significantly reduced 4% at rest and 5% at both submaximal and maximal worklevels (table IXa and figure 13). Note that in both pre and post phlebotomy the oxygen carriage is greatest in exercise. The percentage of oxygen utilized was significantly increased after phlebotomy; at rest 33%, at submaximal 26% and 15% at maximal work (table IXc). The mixed venous oxygen content was reduced 18% at rest, 38% at submaximal and 50% at maximal work (table XIIIa). Oxygen pulse decreased 14% at rest, and 8% at both submaximal and maximal work (table XIIIc).

Hemoglobin (Hb) and Blood Viscosity (η)

Hemoglobin concentration was reduced after phlebotomy by 5% at rest and further reduced 7% at both exercise levels (table IXd). Blood viscosity, measured in subject J.P., was reduced 4% after the post phlebotomy maximal exercise.

Heart Rate (H.R.) and Stroke Volume (S.V.)

Heart rate increased significantly 33% at rest, and 7% and 6% at 70% maximal and maximal exercise in post phlebotomy tests (table XIa). Note the linear rise in H.R. against work level (figure 9), and cardiac output (figure 4), except in post phlebotomy maximal exercise where the H.R. rises sharply, 7%, against a minimal rise in cardiac output (figure 4). A concommitant significant decrease in S.V. was recorded of 27% at rest, and about 24% at both exercise levels in the post phlebotomy states (table XIb). The statistical significance increased from rest to exercise in both pre and post phlebotomy. Submaximal exercise produced the greatest S.V. in the pre and post comparisons.

Blood Volume and Central Blood Volume (C.B.V.)

Total blood volume, estimated indirectly from the plasma volume, was 715 mls. less (10.3 ml./kg.) when measured 25 minutes after post phlebotomy maximal work (table XId). This 12.8% decrease in circulation blood volume indicates a flow of extravascular fluid into the circulation. Furthermore, these four subjects lost a total mean amount of 975 mls. (table II); thus 27.4% of the blood loss was recovered 25 minutes after maximal exercise in the post phlebotomy state. Central blood volume was significantly decreased 17% at post phlebotomy rest and non-significantly decreased 20% and 9% at both post phlebotomy worklevels respectively (table XIc). Note that pre phlebotomy maximal exercise elicited a 10% drop in C.B.V. from the submaximal level but no such drop was recorded in post phlebotomy maximal exercise when cardiac output was 9% lower (figure 15). True mean transit times were nonOsignificantly slower (table XIIa).

Lactate Concentration

Lactic acid amounts measured upon the cessation of exercise rose slightly in post phlebotomy tests at rest and exercise levels (table XIIb).

Arterial Pressures ($\bar{M}ap$, $\bar{M}sp$, $\bar{M}dp$) and Total Periperal Resistance (T.P.R.)

Mean arterial pressure was reduced 15% at rest, 11% at submaximal work and 13% at maximal work in the post phlebotomy investigations (table Xa and figure 14). Accordingly, the mean systolic and diastolic pressures were significantly lower in the post phlebotomy state. Note that mean systolic pressure increased significantly more in exercise over rest than did diastolic pressure at both pre and post worklevels. Mean systolic pressure increased 63% from rest to maximal

exercise in both the pre and post phlebotomy tests (table Xb). Mean diastolic pressure increased from rest to exercise, 18% before phlebotomy and only 11% after phlebotomy.

Total peripheral resistance increased significantly after phlebotomy at rest and increased only very slightly after phlebotomy at both worklevels. There was an identical 65% drop in resistance in the transition to both exercise levels in both pre and post phlebotomy investigations (table Xd).

Table I

Physical Characteristics Of Subjects

Subj.	Age	Height cm.	Weight kg.	Surface Area M^2	Max Work load kg/min	$\dot{V}O_2$ Max Work load l/min	Heart Rate Max Post pH	Previous Blood Donor
JP	28	175	68	1.83	1600	3.75	180	No
PK	22	180	75	1.93	1400	3.00	190	Yes
TG	34	174	65	1.77	1500	3.31	180	Yes
GW	21	179	73	1.91	1200	2.90	195	Yes
RT	51	183	75	1.96	1200	3.03	190	Yes
EB	22	174	68	1.81	1800	3.70	195	Yes
FT	27	173	71	1.83	1200	2.90	180	Yes
Mean	29	177	71	1.86	1414	3.23	187	
SD	9.2	3.5	3.6		217	.33	6.5	

Table II

Amount Of Phlebotomy (Mls.)

Subj.	JP	PK	TG	GW	RT	EB	FT	MEAN
Main* Phlebotomy	680	750	650	730	750	680	710	70.7
Pre Blood Samples	165	125	135	140	140	140	160	
Post Blood Samples	125	125	135	140	140	140	160	
Blood Loss Total (Mls.)	960	1000	920	1000	1020	960	1020	98.30
Mls/Kg.	14.1	13.3	14.2	13.7	13.6	14.1	14.4	13.91

*10 Mls./Kg. taken between the pre and post tests.

Table III

Preliminary Studies

Subj.	Max. VE	Max. S.T.P.D.	$\dot{V}O_2$ L/Min.	Ml/Kg/Min	Max. Workload KPM
JP	120		3.60	53	1700
PK	90		3.15	43	1500
TG	94		3.20	49	1600
GW	97		2.90	40	1400
RT	110		3.00	36	1300
EB	118		3.75	55	1800
FT	112		3.10	45	1400

Table IVa

Pre Phlebotomy Studies

Subj.	Work Load KPM	VE L/Min S.T.P.D.	VO_2	VO_2 Mls/Min/Kg	VCO_2 L/Min	R.Q.	PO_2 MM	PCO_2 Hg	pH
1	Rest	10.1	.33	5	.26	.79	76	26	7.41
	1100	71.2	2.40	35	2.10	.98	84	30	7.33
	1600	134.5	3.76	55	4.49	1.19	82	23	7.30
2	Rest	12.6	.19	3	.18	.92	91	28	7.45
	1100	72.0	2.39	32	2.43	1.02	84	31	7.29
	1400	94.2	3.00	40	3.40	1.13	86	26	7.33
3	Rest	9.0	.20	3	.17	.84	85	32	7.39
	1100	62.1	2.47	38	2.42	.98	81	29	7.34
	1500	98.5	3.31	51	3.58	1.08	90	24	7.21
4	Rest	20.2	.29	4	.24	.83	79	25	7.46
	900	88.8	2.04	28	2.30	1.15	84	28	7.37
	1200	90.3	2.90	40	3.47	1.19	82	27	7.39

Table IVa

Pre Phlebotomy Studies

Subj.	Work Load KPM	VE L/Min S.T.P.D.	VO_2	VO_2 Mls/Min/Kg	VCO_2 L/Min	R.Q.	PO_2 MM	PCO_2 Hg	pH
5	Rest	12.0	.20	3	.25	.75	80	28	7.49
	900	52.9	1.88	25	1.85	.98	82	27	7.43
	1200	117.6	3.03	40	3.62	1.15	84	23	7.39
6	Rest	16.2	.40	6	.40	.72	81	28	7.49
	1200	75.0	2.94	43	2.94	.99	74	29	7.40
	1800	114.0	3.70	55	3.70	1.17	69	30	7.30
7	Rest	12.6	.40	6	.40	.73	77	32	7.41
	900	65.0	2.23	31	2.33	1.06	90	29	7.38
	1200	73.4	2.90	39	2.90	1.15	85	29	7.38

Table IVb

Pre Phlebotomy Studies

Subj.	Work Load KPM	C.O. Dye	C.O. Campbell CO_2	C.O. Wass.F. CO_2	H.R. Max.	S.V. Mls.	T.B.V. Mls.
			L/Min.				
1.	Rest	5.86	5.01	6.58	85	69	
	1100	27.13	22.23	20.00	156	143	
	1600	24.43	26.16	24.37	170	144	
2.	Rest	4.18	5.71	6.92	70	60	
	1100	17.14	20.92	18.99	163	105	
	1400	19.10	19.12	17.95	180	106	
3.	Rest	4.80	5.69	7.30	60	80	
	1100	19.55	17.90	16.30	158	124	
	1500	17.78	16.13	15.30	175	105	5767
4.	Rest	5.06	4.91	5.90	74	69	
	900	17.95	17.39	15.60	165	128	
	1200	17.12	14.94	14.60	180	99	5290

Table IVb

Pre Phlebotomy Studies

Subj.	Work Load KPM	C.O. Dye	C.O. Campbell CO_2 L/Min	C.O. Wass.F. CO_2 L/Min	H.R. Max.	S.V. Mls.	T.B.V. Mls.
5.	Rest	4.67	4.01	4.89	63	74	
	900	16.08	16.55	14.53	157	102	
	1200	15.12	18.54	16.87	180	103	
6	Rest	4.89	5.99	7.35	60	82	
	1200	22.64	17.76	16.33	165	137	
	1800	21.67	18.15	17.46	180	120	5856
7	Rest	4.96	4.66	5.70	53	94	
	900	18.80	19.08	17.10	150	132	
	1200	20.88	14.78	13.76	165	127	5466

Table IVc

Pre Phlebotomy Studies

Subj.	Work Load KPM	O_2 Sat.%	C_aO_2 Ml/100 ml.	% O_2 Util.	A-V O_2 Dif.	Hb gm/ 100 mls.	COHb %	Lact. mg.%
1.	Rest	99.6	21.1	28	56	15.0		7.70
	1100	94.5	21.3	51	108	16.0		24.77
	1600	96.1	21.6	71	153	16.2		52.87
2.	Rest	97.0	20.3	20	45	14.8	1.2	1.18
	1100	99.0	22.3	62	139	16.0	1.4	44.80
	1400	97.5	21.5	73	157	15.7	1.5	58.63
3.	Rest	97.0	20.8	20	41	15.2	1.0	1.62
	1100	98.0	22.5	56	126	16.3	2.0	29.80
	1500	98.4	22.8	82	186	16.5	.7	56.87
4.	Rest	97.8	20.3	28	57	14.7	3.0	3.16
	900	98.3	21.0	54	114	15.2	2.8	26.07
	1200	97.3	21.1	80	169	15.4	2.8	39.23

Table IVc

Pre Phlebotomy Studies

Subj.	Work Load KPM	O_2 Sat.%	C_aO_2 Ml/100 ml.	$\%O_2$ Util.	A-V O_2 Dif.	Hb gm/ 100 mls.	COHb %	Lact. mg.%
5.	Rest	98.4	20.4	21	43	14.8	2.2	2.38
	900	96.6	21.0	56	117	15.5	2.2	24.77
	1200	98.6	21.7	79	178	15.7	1.7	51.56
6.	Rest	98.6	21.8	32	69	15.8	2.3	1.53
	1200	97.5	22.4	58	130	16.4	2.3	21.77
	1800	95.2	24.7	69	170	17.0	2.1	56.09
7.	Rest	97.9	20.5	39	79	14.9	2.7	.62
	900	98.6	22.1	69	118	16.0	2.5	25.50
	1200	98.4	22.5	62	139	16.3	2.5	31.48

Table IVd

Pre Phlebotomy Studies

Subj.	Work Load KPM	C.B.V. l	T.M.T.T. Sec	M.T.T. Sec	M.A.P. mm	Art.Pr. Hg	T.P.R.
1.	Rest	1.11	12.5	5.5	90	114/70	.92
	1100	3.79	8.4	4.6	112	168/78	.30
	1600	3.05	7.6	3.8	120	180/95	.30
2.	Rest	1.04	15.6	8.4	92	123/75	1.00
	1100	2.04	6.8	3.7	114	165/75	.40
	1400	2.08	6.7	3.3	106	167/75	.33
3.	Rest	1.10	14.2	7.5	82	100/70	1.03
	1100	1.59	5.3	3.4	102	145/75	.31
	1500	1.57	4.8	3.6	105	150/80	.36
4.	Rest	1.43	15.1	7.5	90	130/68	.88
	900	2.19	7.3	3.8	108	164/80	.36
	1200	2.12	7.3	5.5	106	164/76	.37

Table IVd

Pre Phlebotomy Studies

Subj.	Work Load KPM	C.B.V. l	T.M.T.T. Sec.	M.T.T. Sec.	M.A.P. mm	Art.Pr. Hg	T.P.R.
5.	Rest	1.28	17.0	11.6	86	112/72	1.10
	900	2.55	8.6	5.6	104	152/76	.39
	1200	1.93	7.7	6.0	114	176/84	.37
6.	Rest				88	116/72	
	1200				112	160/72	.30
	1800				115	184/80	.32
7.	Rest	1.6	19.5	9.5	90	128/68	1.08
	900	2.0	6.5	3.8	112	164/68	.36
	1200	1.99	5.8	3.4	124	192/88	.36

Table Va

Post Phlebotomy Studies

Subj.	Work Load KPM	VE L/Min S.T.P.D.	VO_2	VO_2 Mls/Min/Kg	VCO_2 L/Min	R.Q.	PO_2 mm	PCO_2 Hg	pH
1.	Rest	17.8	.38	6	.34	.88	78	29	7.38
	1100	81.5	2.35	35	2.55	1.09	78	28	7.35
	1600	127.3	3.73	55	4.17	1.15	96	25	7.22
2.	Rest	17.5	.21	4	.20	.89	88	24	7.44
	1100	90.3	2.40	31	2.60	1.08	102	26	7.28
	1400	108.3	3.04	41	3.33	1.15	88	25	7.30
3.	Rest	15.7	.30	5	.23	.77	77	30	7.40
	1100	78.0	2.28	35	2.80	1.00	95	28	7.28
	1500	115.8	3.19	47	3.79	1.25	97	21	7.21
4.	Rest	14.2	.35	5	.23	.80	79	26	7.48
	900	88.5	2.06	28	2.70	1.17	73	30	7.42
	1200	91.7	2.84	39	3.10	1.11	76	27	7.41

Table Va

Post Phlebotomy Studies

Subj.	Work Load KPM	VE L/Min S.T.P.D.	VO_2	VO_2 Mls/Min/Kg	VCO_2 L/Min	R.Q.	PO_2 mm	PCO_2 Hg	pH
5.	Rest	8.8	.25	3	.19	.76	76	29	7.46
	900	80.6	1.97	26	2.13	1.08	87	22	7.48
	1200	108.7	2.81	40	3.23	1.09	86	21	7.41
6.	Rest	22.0	.33	5	.33	.91	83	31	7.44
	1200	71.6	2.71	40	2.71	1.04	72	29	7.40
	1800	111.0	3.55	52	3.55	1.15	73	28	7.35
7.	Rest	18.4	.47	7	.47	.89	78	35	7.41
	900	83.6	2.34	33	2.34	1.10	95	23	7.47
	1200	80.3	2.95	41	3.25	1.14	84	26	7.42

Table Vb

Post Phlebotomy Studies

Subj.	Work Load KPM	C.O. Dye	C.O. Campbell CO_2	C.O. Wass.F. CO_2	H.R. Max.	S.V. Mls.	T.B.V. l.
		L/Min.					
1.	Rest	4.60	3.66	4.46	90	51	
	1100	17.17	15.11	13.95	170	101	
	1600	21.09	21.53	20.04	180	117	
2.	Rest	5.40	6.34	7.60	86	63	
	1100	16.79	17.09	15.79	180	93	
	1400	14.56	17.02	15.89	190	77	
3.	Rest	3.68	4.23	5.20	90	41	
	1100	17.60	17.67	16.50	162	109	
	1500	17.66	17.79	16.70	180	99	5245
4.	Rest	4.66	5.74	7.00	85	55	
	900	12.76	12.75	11.40	175	73	
	1200	14.63	15.90	14.80	195	75	4595

Table Vb

Post Phlebotomy Studies

Subj.	Work Load KPM	C.O. Dye	C.O. Campbell CO_2	C.O. Wass.F. CO_2	H.R. Max.	S.V. Mls.	T.B.V. l.
		L/Min					
5.	Rest	3.96	3.38	3.97	90	44	
	900	11.22	13.74	12.33	165	69	
	1200	12.07	14.90	13.70	190	67	
6.	Rest	7.27	6.43	7.90	80	91	
	1200	17.64	17.73	16.46	180	98	
	1800	17.78	14.40	13.92	196	95	4977
7.	Rest	3.88	4.62	6.00	98	40	
	900	18.42	16.45	14.90	160	117	
	1200	15.32	14.99	13.96	180	86	4726

Table Vc

Post Phlebotomy Studies

Subj.	Work Load KPM	O_2 Sat.%	C_aO_2 Ml/100 ml.	% O_2 Util.	A-V O_2 Dif.	Hb gm/ 100 mls.	CO Hb %	Lact. mg.%
1.	Rest	98.2	20.4	41	83	14.6		16.16
	1100	95.3	20.9	67	136	15.6		21.58
	1600	98.5	21.5	79	172	15.4		55.23
2.	Rest	97.1	19.5	20	39	14.3	1.5	1.20
	1100	98.0	19.7	73	143	14.3	1.0	38.85
	1400	98.3	20.3	88	179	15.0	1.6	58.33
3.	Rest	98.5	20.3	40	81	14.7	2.0	1.37
	1100	98.6	21.5	67	130	15.6	1.1	36.81
	1500	98.5	21.4	83	181	15.5	1.2	65.57
4.	Rest	99.0	20.1	37	75	13.7	2.7	1.24
	900	97.7	19.6	82	161	14.4	2.6	26.50
	1200	97.8	20.2	90	182	14.8	2.3	45.36

Table Vc

Post Phlebotomy Studies

Subj.	Work Load KPM	O_2 Sat.%	C_aO_2 Ml/100 mls.	% O_2 Util.	A-V O_2 Dif.	Hb gm/ 100 mls.	CO Hb %	Lact. mg.%
5.	Rest	98.2	19.6	31	63	14.2	2.0	4.49
	900	98.7	20.5	85	175	14.8	1.7	27.22
	1200	98.2	20.6	91	188	14.9	1.6	51.95
6.	Rest	98.2	19.8	23	45	14.2	2.1	5.43
	1200	96.4	21.4	72	153	15.2	2.0	29.87
	1800	95.7	23.4	79	184	16.0	1.6	55.00
7.	Rest	98.5	20.1	60	121	14.7	2.5	2.34
	900	99.8	20.5	62	127	14.7	2.4	26.80
	1200	99.2	20.6	89	192	15.0	2.1	34.25

Table Vd

Post Phlebotomy Studies

Subj.	Work Load KPM	C.B.V. l	T.M.T.T. Sec.	M.T.T. Sec.	M.A.P. mm	Art.Pr. Hg.	T.P.R.
1.	Rest	1.09	14.2	7.8	79	105/66	1.03
	1100	2.67	9.1	5.1	105	171/70	.36
	1600	2.91	8.3	4.5	104	180/66	.30
2.	Rest	1.02	17.8	10.2	75	96/57	.96
	1100	2.09	7.5	4.9	90	145/62	.32
	1400	1.96	8.0	5.3	98	158/70	.40
3.	Rest	.83	15.4	9.4	67	80/60	1.10
	1100	1.70	5.8	4.4	100	150/70	.34
	1500	1.54	5.5	4.5	100	150/70	.34
4.	Rest	1.01	12.0	7.5	76	96/66	.97
	900	1.51	7.03	4.4	92	144/64	.43
	1200	1.38	5.31	3.5	93	144/68	.38

Table Vd

Post Phlebotomy Studies

Subj.	Work Load KPM	C.B.V. l	T.M.T.T. Sec.	M.T.T. Sec.	M.A.P. mm	Art.Pr. Hg.	T.P.R.
5.	Rest	1.06	14.9	8.9	80	96/68	1.21
	900	1.44	7.3	5.8	96	156/68	.51
	1200	1.83	8.8	6.0	98	156/72	.49
6.	Rest				76	108/60	
	1200				98	164/64	.33
	1800				100	160/68	.34
7.	Rest	1.25	18.61	9.1	76	100/60	1.17
	900	1.93	7.01	4.5	96	156/68	.31
	1200	1.91	7.14	4.8	96	160/68	.38

Table VI

Five Day Post Phlebotomy Studies

Subj.	Work Load K.P.M.	VO_2 L/Min S.T.P.D.	VO_2 Ml/Min/Kg	C.O. Campbell CO_2
1.	Rest	.24	3	4.50
		2.50	37	23.20
		3.60	53	26.80
2.	Rest	.31	5	6.40
		2.30	34	17.2
		3.06	45	20.8
3.	Rest	.18	3	5.36
		2.64	41	19.50
		3.10	48	19.60
4.	Rest	.31	4	5.50
		2.18	30	16.50
		2.60	36	17.00
6.	Rest	.40	6	5.85
		2.90	43	21.46
		3.75	55	20.60
7.	Rest	.32	5	
		2.28	33	
		2.90	41	

Table VII a		Rest	Sub Max	Max Ex
Oxygen Uptake (liters/minute)*	Pre $\bar{X}$	.287	2.34	3.23
	Post $\bar{X}$	.327	2.30	3.16
	SD d	.05	.18	.09
	SE	.02	.05	.04
	P	N.S.	N.S.	N.S.
Table VII b				
Oxygen Uptake (mls./kilogram/ minute)*	Pre	4.3	33.1	45.7
	Post	5.0	32.6	45.0
	SD d	.96	1.9	2.1
	SE	.31	.7	.8
	P	N.S.	N.S.	N.S.
Table VII c				
Oxygen Uptake (liters/minute) 6 subjects	Pre	.302	2.41	3.26
	5 Days Post	.293	2.48	3.17
	SD d	.08	.1	.15
	SE	.03	.0	.06
	P	N.S.	N.S.	N.S.
Table VII d				
Oxygen Uptake (mls./kilogram/ minute) 6 subjects	Pre	4.5	34.5	46.6
	5 Days Post	4.3	36.3	46.3
	SD d	1.3	1.0	3.4
	SE	.5	.4	1.4
	P	N.S.	**	N.S.

* Statistical analysis on 7 subjects (42 values)

Table VIIIA		Rest	Sub Max	Max Ex
Cardiac Output Dye Dilution (liters/minute)*	Pre $\bar{X}$	4.9	19.2	19.7
	Post $\bar{X}$	4.4	15.9	16.2
	SD d	.9	2.3	1.9
	SE	.4	.9	.5
	P	N.S.	**	**

Table VIII b		Rest	Sub Max	Max Ex
Cardiac Output - CO_2 Campbell Method (liters/minutes) Pre v.s. 5 days post 5 subjects	Pre	5.5	19.2	18.9
	Post	5.5	19.6	21.0
	SD d	.5	2.8	1.0
	SE	.2	1.3	.5
	P	N.S.	N.S.	*

Table VIII c	All Values	
Cardiac Output - CO_2 Campbell Method v.s. Dye Dilution on all values (l/min)*	CO_2	13.26
	Dye	13.52
	SD d	2.13
	SE	.33
	P	N.S.
	r	.95

Table VIII d	All Values	
Cardiac Output - Campbell CO_2 Method v.s. Campbell CO_2 Method with Wasserman Factor (l/min)*	Campbell CO_2	13.45
	CO_2 Wasserman Factor	12.75
	SD d	2.4
	SE	.4
	P	.10 level

		Rest	Sub Max	Max Ex
Table IX a Arterial Oxygen Content** (mls/100 mls. whole blood)*	Pre $\bar{X}$	20.7	21.8	22.2
	Post $\bar{X}$	19.9	20.6	21.1
	SD d	6	7	5
	SE	2	3	2
	P	**	**	**
Table IX b Arterial-Venous Oxygen Difference (mls. oxygen/100 ml. whole blood)*	Pre	5.6	12.2	16.4
	Post	7.2	14.6	18.3
	SD d	2.4	2.1	1.7
	SE	.9	.8	.7
	P	N.S.	*	*
Table IX c Oxygen Utilized (%)*	Pre	27.0	58.0	73.7
	Post	36.0	73.0	84.4
	SD d	10.7	12.1	7.3
	SE	4.0	4.6	2.8
	P	N.S.	*	**
Table IX d Hemoglobin Concentration (grams/100 mls. whole blood)*	Pre	15.0	15.9	16.1
	Post	14.3	14.9	15.2
	SD d	.5	.4	.2
	SE	.2	.2	.1
	P	**	**	***

** Arterial O_2 Content = 1.39 x Hb(gms.) x Art. O_2 Sat.

Table X a		Rest	Sub Max	Max Ex
	Pre $\bar{X}$	88.3	109	113
Mean Arterial	Post $\bar{X}$	75.6	97	98
Pressure	SD d	3.5	7.3	7.3
(mm. Hg.)*	SE	1.3	2.8	2.8
	P	***	**	**
Table X b	Pre	118	160	173
Mean Systolic	Post	97	155	158
Pressure	SD d	10	11	12
(mm. Hg.)*	SE	3	4	5
	P	**	N.S.	*
Table X c	Pre	71	75	83
Mean Diastolic	Post	62	67	69
Pressure	SD d	6	5	8
(mm. Hg.)*	SE	2	2	3
	P	**	**	**
Table X d	Pre	1.00	34.6	34.4
Total Peripheral	Post	1.07	37.1	37.6
Resistance	SD d	.05	.07	4.8
(Peripheral Resistance	SE	.02	.03	1.8
Units)**	P	*	N.S.	N.S.

** Calculated from Mean Arterial Pres. Gradient

C.O. mls./sec.

Table XI a		Rest	Sub Max	Max Ex
Heart Rate Maximum (Beats/minute)*	Pre $\bar{X}$	66	159	176
	Post $\bar{X}$	88	170	187
	SD d	13.3	4.4	4.0
	SE	5.0	1.7	1.5
	P	**	***	***
Table XI b Stroke Volume (Milliliters/beat)* at Max Heart Rate	Pre	75	124	115
	Post	55	94	88
	SD d	22	16	11
	SE	8	6	4
	P	*	**	***
Table XI c Central Blood Volume (liters)* 6 subjects	Pre	1.26	2.36	2.12
	Post	1.04	1.89	1.92
	SD d	.16	.57	.26
	SE	.1	.2	.1
	P	*	N.S.	N.S.

Table XI d		Total Blood Volume
Total Estimated Blood Volume and Blood Volume Decrease After Testing mls.*	Pre	5595
	Post	4886
	SD d	147
	SE	74
	P	**
Mean Blood Loss mls.		709.0
mls./kg.		10.3

Table XII a		Rest	Sub Max	Max Ex
True Mean Transit Time (seconds) 6 subjects	Pre $\bar{X}$	15.6	7.2	6.7
	Post $\bar{X}$	15.5	7.3	7.2
	SD d	2.2	.8	1.3
	SE	.9	.3	.5
	P	N.S.	N.S.	N.S.
Table XII b Lactate Concentration (milligrams %)*	Pre	2.6	28.2	49.5
	Post	4.6	29.7	52.2
	SD d	3.4	5.1	3.6
	SE	1.3	1.9	1.4
	P	N.S.	N.S.	N.S.
Table XII c Volume Expired (Liters/minute S.T.P.D.)*	Pre	13.2	69.6	103.2
	Post	16.3	82.0	106.2
	SD d	5.4	11.1	10.2
	P	N.S.	*	N.S.

Table XIII a		Rest	Sub Max	Max Ex
Mixed Venous Oxygen Content milliliters/100 mls. blood	Pre $\bar{X}$	15.2	9.6	5.8
	Post $\bar{X}$	12.7	5.9	2.9
	SD d	2.0	1.8	2.0
	SE	.7	.7	.8
	P	*	**	**
Table XIII b Respiratory Quotient	Pre	.79	1.02	1.15
	Post	.84	1.08	1.14
	SD d	.1	.03	.08
	SE	.04	.01	.03
	P	N.S.	**	N.S.
Table XIII c Oxygen Pulse (Millileters O_2/Heart Beat)**	Pre	4.3	14.7	18.4
	Post	3.7	13.5	16.9
	% Decrease	14.0	8.0	8.2

* * $\frac{\text{Mean } VO_2 \text{ mls.}}{\text{Mean Max. H.R.}}$

DISCUSSION

This study attempted to quantitatively measure the physiological parameters involved in the oxygen uptake by the body before and after a phlebotomy of 10 mls./kg. of body weight. The subjects chosen represent a fair cross-section of healthy young men and one older physically active man.

All of the earlier recorded studies investigating the effect of phlebotomy upon oxygen uptake or work capacity phlebotomized their subjects 500 mls. of blood. Parameters measured generally included oxygen uptake values, performance times and heart rates. Statistically significant changes were few and no attempts were made to measure the many physiological determinants of the oxygen transport and uptake system. It was decided that a phlebotomy of 10 mls./kg. would be required to produce significant changes in the oxygen transport system that could be quantitatively measured.

There was a wide variability in the "cardio-respiratory fitness" of the subjects as shown in Table III. At the time of testing, subjects J. P., T. G., and E. B. were all engaged in fitness training programs resulting in high oxygen uptakes (mls./kg.).

The oxygen uptake values did not change significantly in the post phlebotomy tests either on the day of the phlebotomy or five days later. The same amount of external work was done in the pre and post tests; the workload and time of exertion remained constant. Assuming the same metabolic pattern and working efficiency, then the oxygen uptake values should be similar. Bicycle work mainly involves the working

muscles of the legs although at high work levels, muscles in the back, shoulders and arms may come into extensive use by pulling on the handle bars. Some of the variations in the oxygen uptake may be attributed to this upper body work. When the legs are close to exhaustion and increasing in anaerobic work the upper body muscles may be further employed to pull some of the load, thus increasing total body oxygen uptake. After phlebotomy the circulating catecholamine level is usually increased and the resulting calorigenic effect could cause an increased oxygen uptake in the resting state. Also, an increase in the oxygen uptakes of some subjects at rest may have been caused by their increased activity in order to avoid fainting. Motivation and psychological states do not affect the maximal physiological responses; i.e., heart rate, ventilation, oxygen uptake or oxygen pulse.[83] However a subject might be able to increase anaerobic capacity by increasing tolerance to anaerobic metabolites and thus perform for a longer time. All the subjects complained of more fatigue during post phlebotomy maximal rides even though oxygen uptakes were not significantly reduced. Lactate values were slightly higher after all post phlebotomy worklevels.

Cardiac output and hemoglobin concentration determine the capacity for oxygen transport providing normal oxygen saturation is possible. Cardiac output at rest was not significantly reduced probably due to the increased movements of some subjects. In two subjects an insufficient cardiac output, presented by a slow heart rate, caused collapse during post phlebotomy resting measurements. This vasovagal reaction was preceded by a low heart rate (under 60 beats/min.). The mean heart rate

was increased 33% at rest although a concommitant decrease in stroke volume was measured. After hemorrhage there is a decreased venous return owing to an actual reduction in blood volume, or to blood pooling in the lower part of the body. The arterial pressure falls and the baroreceptors are stimulated to inhibit the cardioinhibitory center with the consequent increase in heart rate. Stroke volume is controlled largely by: (1) effective filling pressure, (2) Contractility, (3) ventricle distensibility and (4) the systemic arterial blood pressure. After hemorrhage we measured a significantly decreased arterial pressure. Total peripheral resistance was increased slightly indicating a greater decrease in cardiac output than concommitant maintenance of arterial pressure in the face of blood loss. At rest there was an insufficient response by the vasomotor center to maintain normal cardiac output.

During exercise at both submaximal and maximal worklevels the cardiac output was reduced despite increases in heart rate. Stroke volume and mean arterial pressures were lower. Therefore the afterload was decreased upon the heart and yet a reduced venous return is probably responsible for the decreased cardiac output. Right atrial pressure was not measured. The increase in sympathetic discharge resulting indirectly from phlebotomy and directly from exercising muscles causes an increase in epinephrine and norepinephrine release from the adrenal medulla and adrenergic nerve endings. Construction of arterioles in many vascular beds, especially in the skin, mucosa and splanchnic region helps to maintain arterial pressure. However, there is a marked increase

in blood flow to skeletal muscle due to a powerful B-receptor vasodilator action. Norepinephrine in small amounts is not sufficient to cause constriction of the vascular system supplying the working muscles. Opposite physiological forces are in effect, since after phlebotomy muscle blood flow tends to decrease but exercising muscles require an increased blood flow, and cutaneous tissues should require an increase in flow to dissipate heat. Central blood volume was significantly decreased at rest but did not significantly change during the two worklevels. These effects must have been due to translocation of blood volume to the working muscles from the splanchnic circulation and capacitance vessels with a sparing of the central blood volume so necessary for the cardiac musculature and pulmonary oxygenation of the blood. If the body core temperature (which was not measured) had risen non-proportionately higher for a given worklevel, evidence would be present to indicate a decreased cutaneous blood flow.

The total body capacity for oxygen mainly determined by the blood volume, hemoglobin concentration, myoglobin, diffusing capacity of the lungs and capability of saturation of a normal O_2 dissociation curve for the physiological state of the blood, i.e., pH, temperature and CO_2 content. Hemoglobin concentration was significantly reduced indicating that hemodilution was occurring (27% of the blood volume had been replaced 25 minutes after maximal post phlebotomy exercise) although there was an increase in hemoglobin concentration from rest to exercise in the pre and post tests due to a loss of intra-vascular fluid to the interstitial spaces. Oxygen saturation remained high after phlebotomy. Arterial oxygen content was reduced proportionately to the hemoglobin changes at

all respective post phlebotomy tests. Therefore with a reduction in total blood volume, arterial oxygen content and cardiac output, the only means of maintaining the oxygen uptake is an increased arterial-venous oxygen difference. This is borne out by the respective increase in the percentage oxygen utilization and decrease in oxygen content of mixed venous blood. These changes become more significant as exercise increases to maximal levels at which the mean percentage oxygen utilized reaches 84.4. The shifting of the oxygen dissociation curve to the right with temperature rise, pH drop and increased CO_2 production enhances the drop off of oxygen in the tissues and the resulting high oxygen utilization percentage.

As hemodilution progresses, blood viscosity decreases due to the drop in hematocrit. In one subject (J. P.) blood viscosity was decreased four percent at the time of post phlebotomy maximal exercise. The following formula from McClelland[80] was employed to measure the change in blood viscosity:

$$\eta \text{ Relative Viscosity} = \frac{c\rho t}{c\rho_o t_o}$$

c = constant depending on the dimensions of the capillary (Oswald viscometer)

ρ = density of pre infusion blood

ρ_o = density of post infusion blood

t = time for pre infusion blood

t_o = time for post infusion blood

The densities of the pre and post phlebotomy blood during maximal exercise were 1.070 and 1.061 gm. cc. respectively and the time in seconds for the blood to drain through the viscometer were 240 seconds and 232 seconds respectively.

$$\eta_{rel} = \frac{(1.070)\ (240)}{(1.061)\ (232)} = 1.04$$

Cardiac output comparisons were made between the dye dilution curves and Campbell's CO_2 rebreathing method[43] on all pre and post phlebotomy tests. Cardiac outputs were also performed five days after phlebotomy with the Campbell CO_2 method. A correlation coefficient of .95 was found and 96% of all the comparisons fell within $\pm$ 20% of the line of identity (Figure 11). There was a tendency for CO_2 rebreathing values for cardiac output to be high at rest but at exercise levels the means were very close although the values were often 10% to 15% apart. Preliminary studies compared various combinations of rates and depths of breathing patterns. It is essential that the rate and depth of breathing bring about rapid mixing of the bag and lung contents during equilibrium rebreathing before recirculation brings back exogenous CO_2.

The PCO_2 during equilibrium between the gas in the rebreathing bag and lungs system and blood in the pulmonary capillaries may be estimated in three ways: recognition of an equilibrium pattern, by interpolation formula or extrapolation methods.[43] During exercise, concentrations of 15% and 17% CO_2 were used. Subjects became dizzy and air starved after the first bag and if a second bag was required it usually terminated the ride if the level was maximal. The high con-

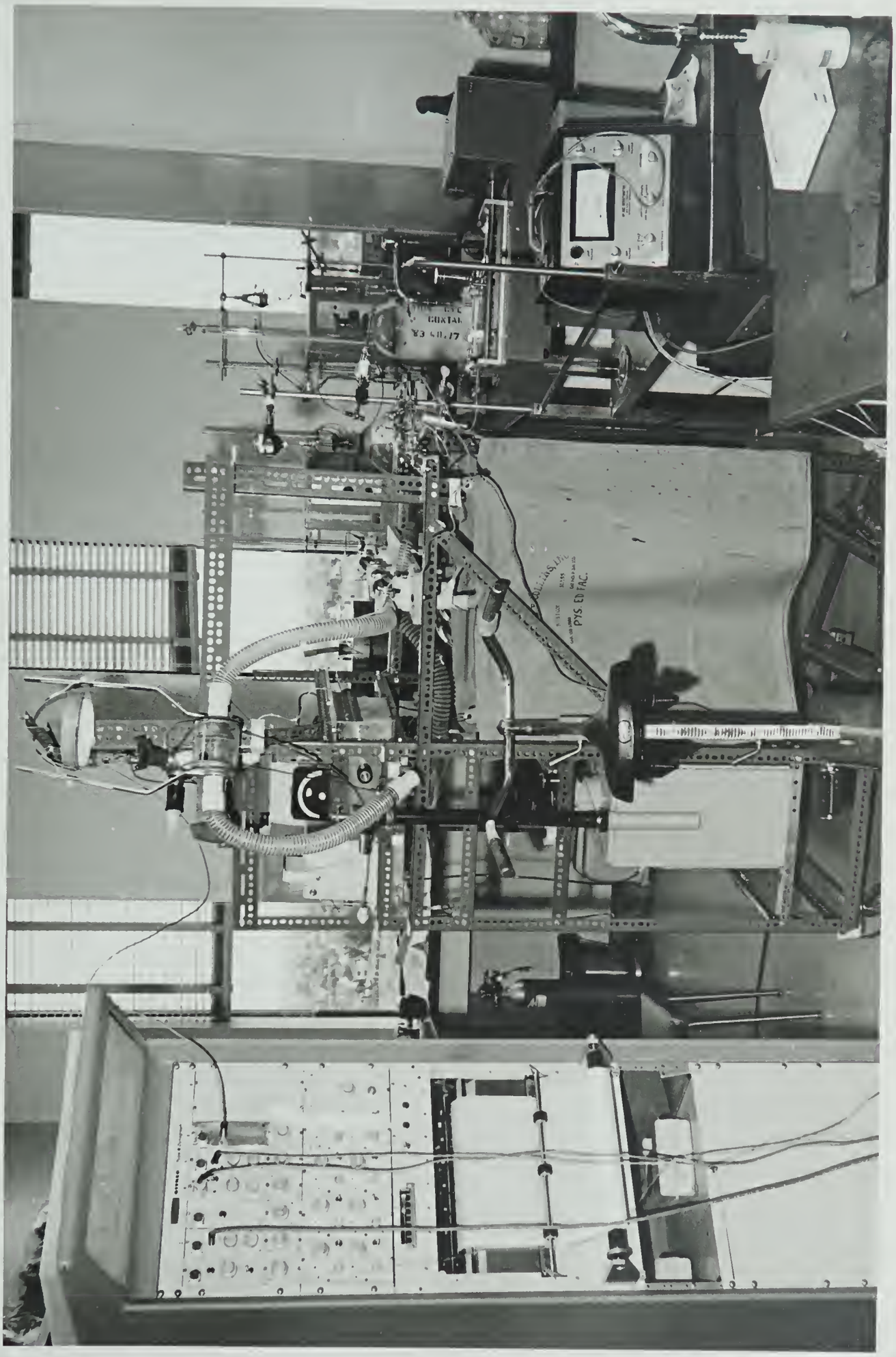
centration of CO_2 and collapsing tendency of the rebreathing bag at high flow rates made it difficult for the subjects to breathe and contributed to their dizziness. End tidal air was measured to estimate the PCO_2 of the arterial blood. End alveolar air was also measured and was usually 1% higher, possibly due to recirculation if the expiration was long; more likely it was a truer estimate of Pa_{CO_2} than was end tidal air. End tidal air was used to determine Pa_{CO_2} from which the best results were received.

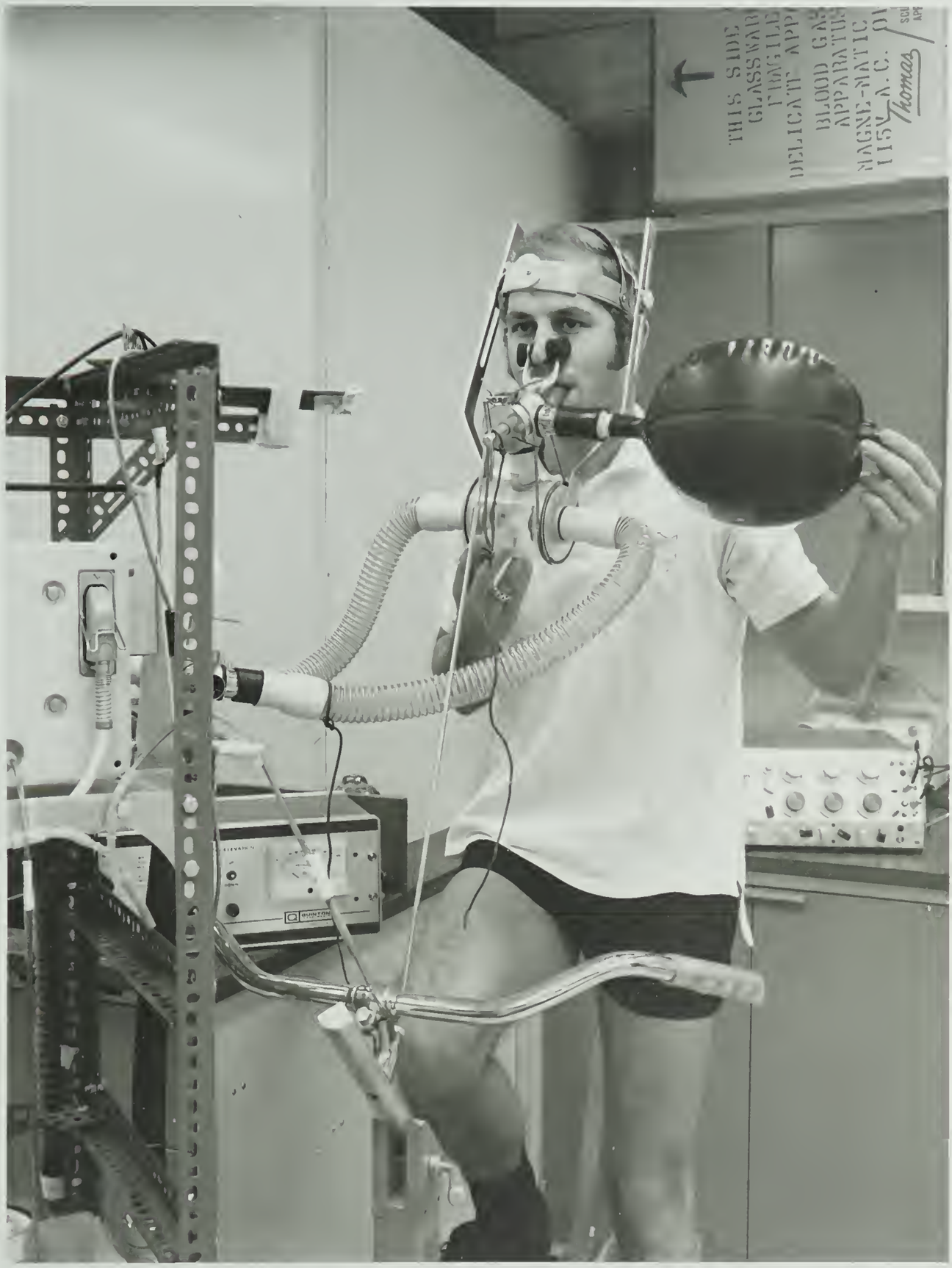
The CO_2 Campbell method versus dye dilution curves was a linear relationship. The regression equations were:

$$\text{Campbell } CO_2 = \text{Dye dilution } (.889) + 1.189$$

$$\text{Dye dilution} = \text{Campbell } CO_2\ (1.029) - .149$$

The effect of rebreathing high concentrations of CO_2 did not affect dye dilution curves when the two methods were performed simultaneously although only a few comparisons were made. Reproducibility of cardiac outputs was excellent using the Campbell method.

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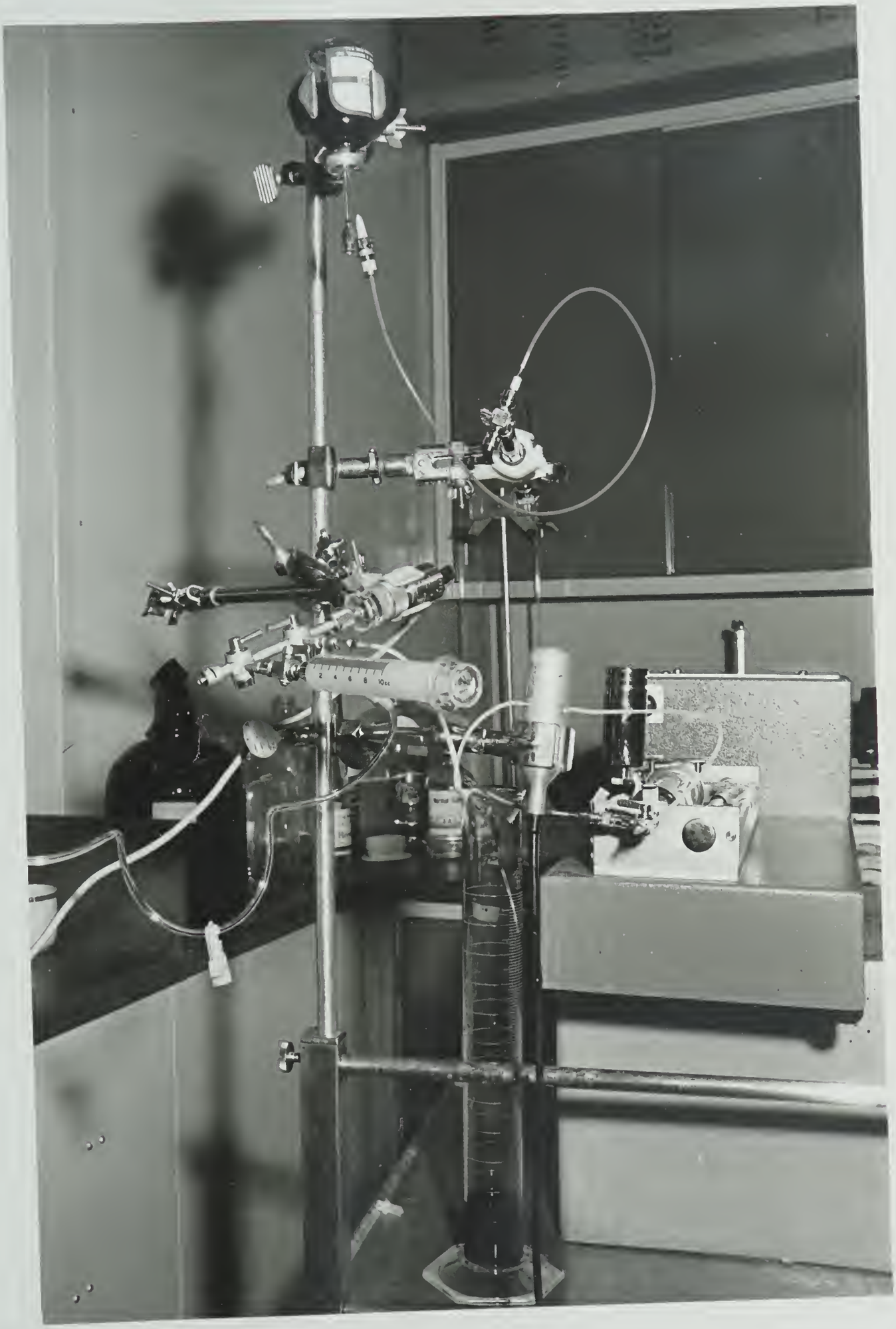


Graph for the Estimation of Submaximal and Maximal Oxygen Uptake Values and their Corresponding Worklevels from Preliminary Tests.

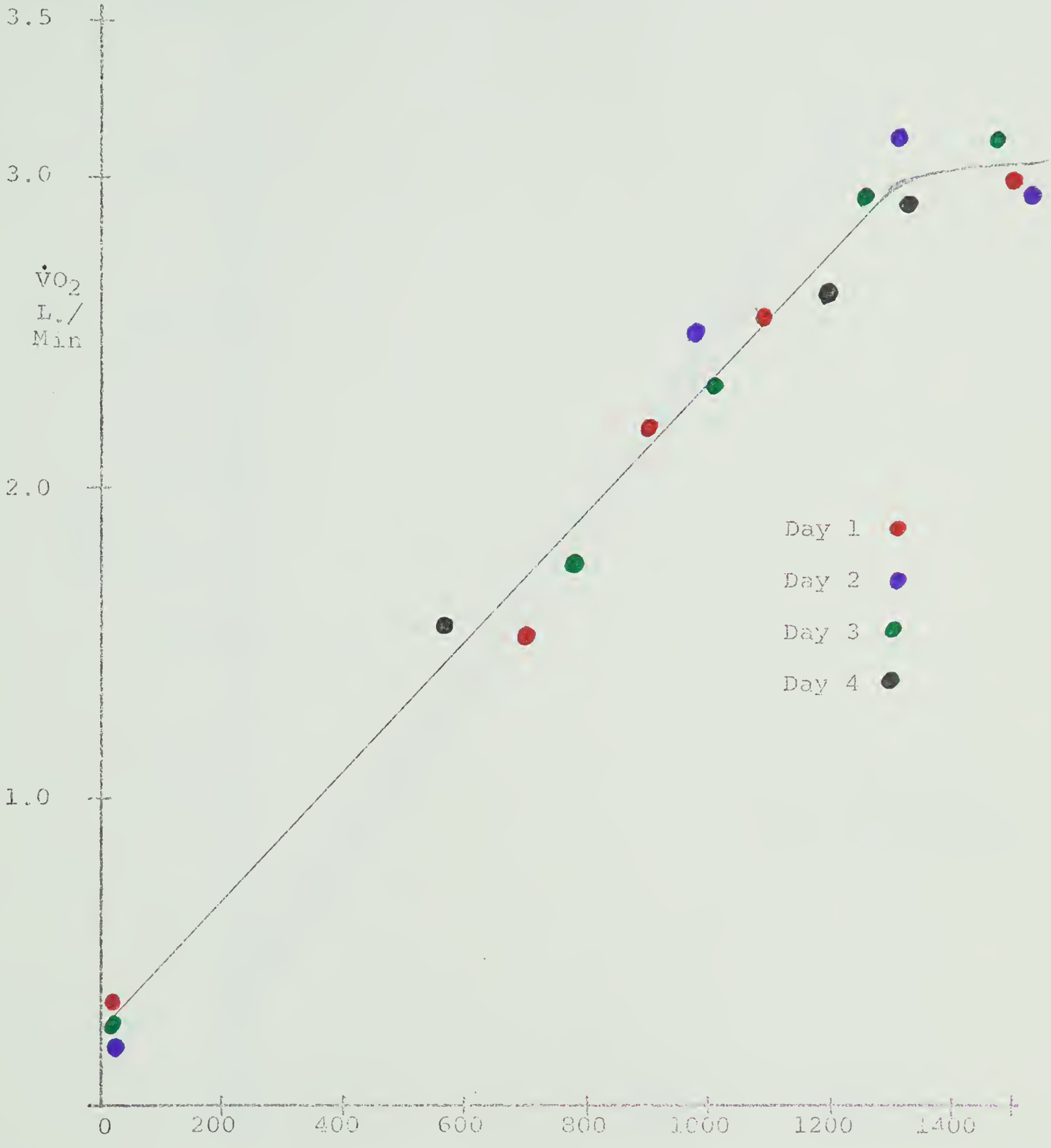


Figure 4

Relationship Between Oxygen Uptake and Worklevel

Figure 5

Relationship Between Cardiac Output (Dye) and Worklevel

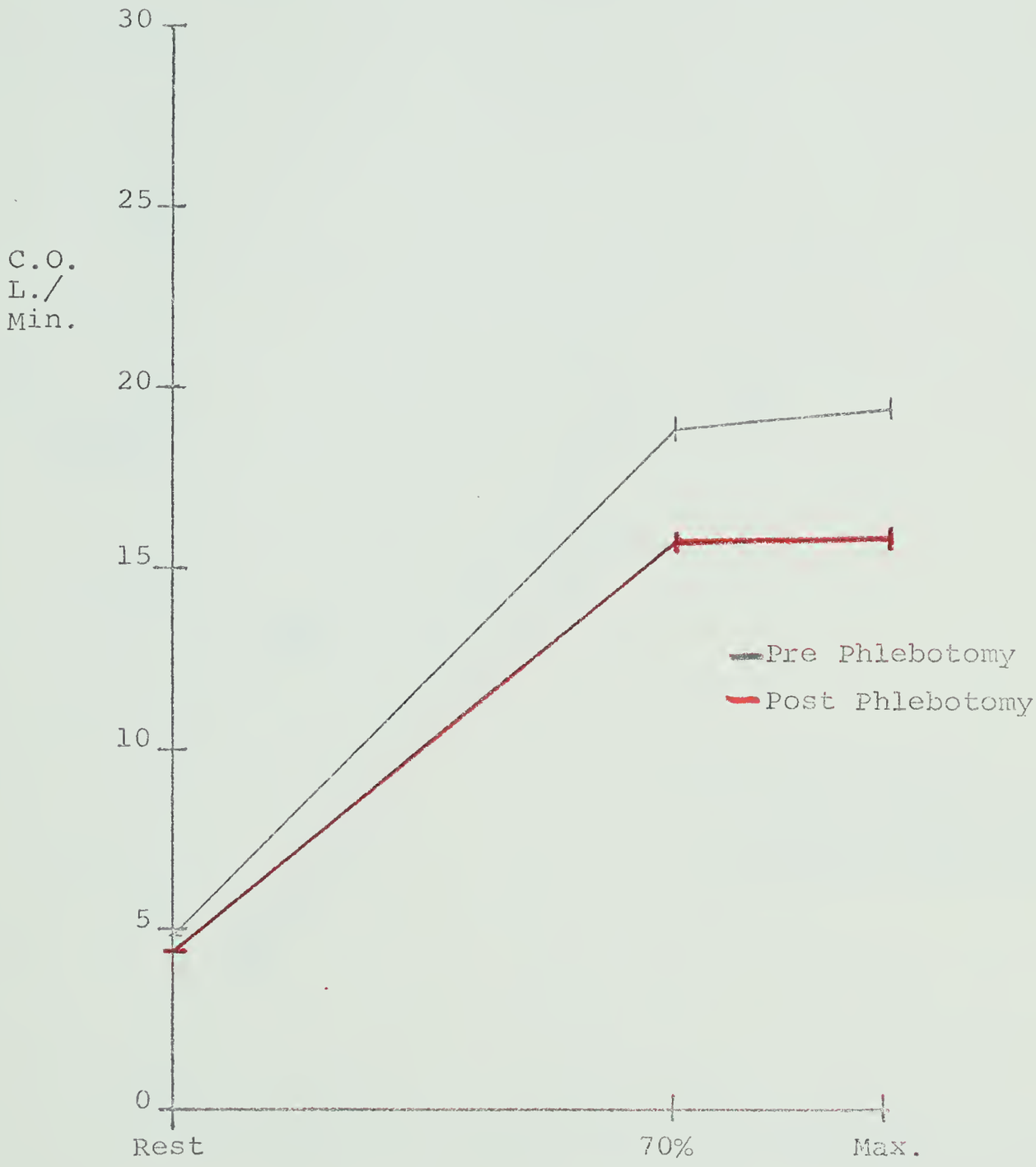


Figure 6

Relationship Between Cardiac Output (Dye) and Oxygen Uptake at Rest, 70% and Max. Worklevel

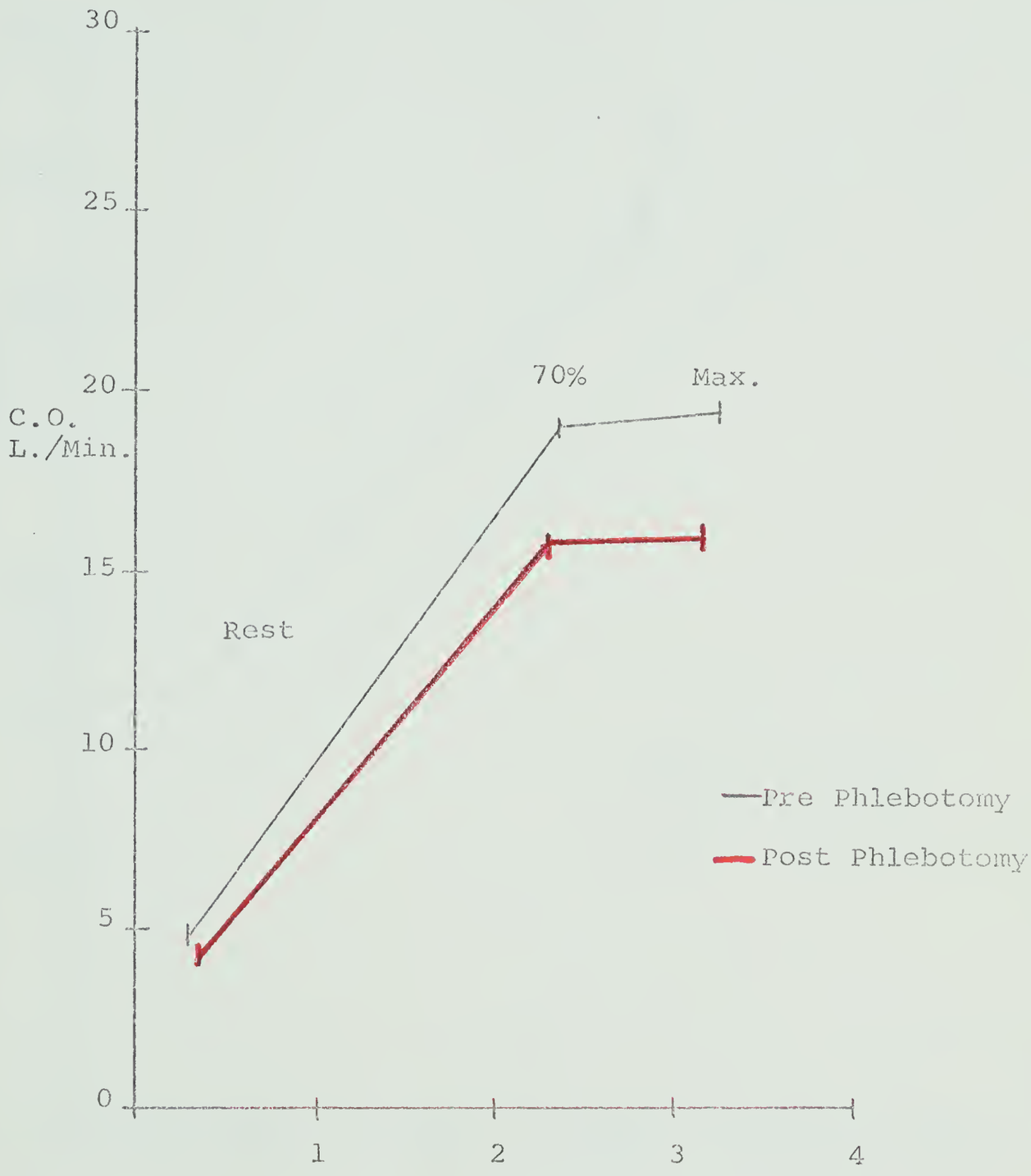


Figure 7.

Relationship Between Cardiac Output and Heartrate

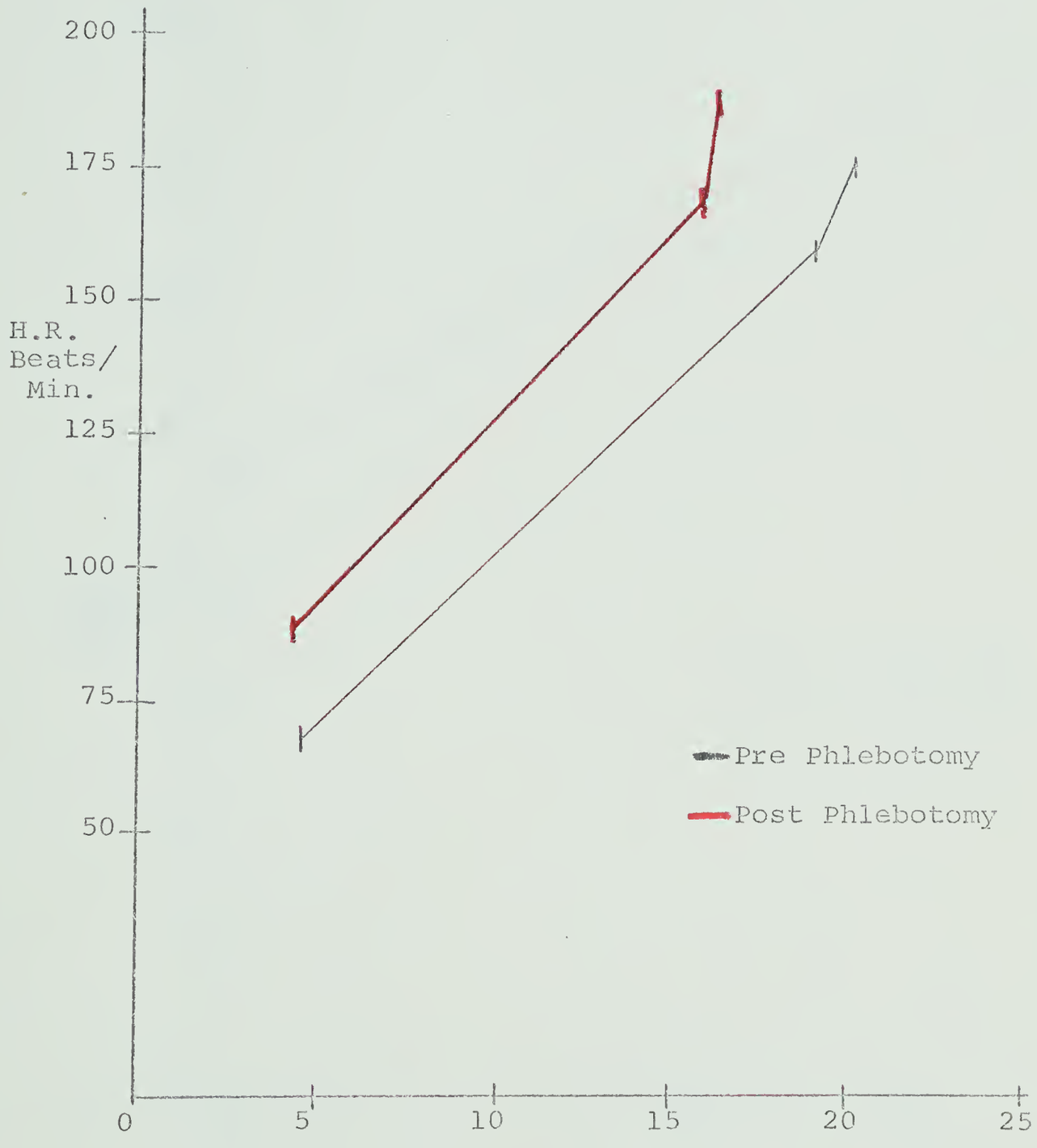


Figure 8

Relationship Between Heartrate and Worklevels.

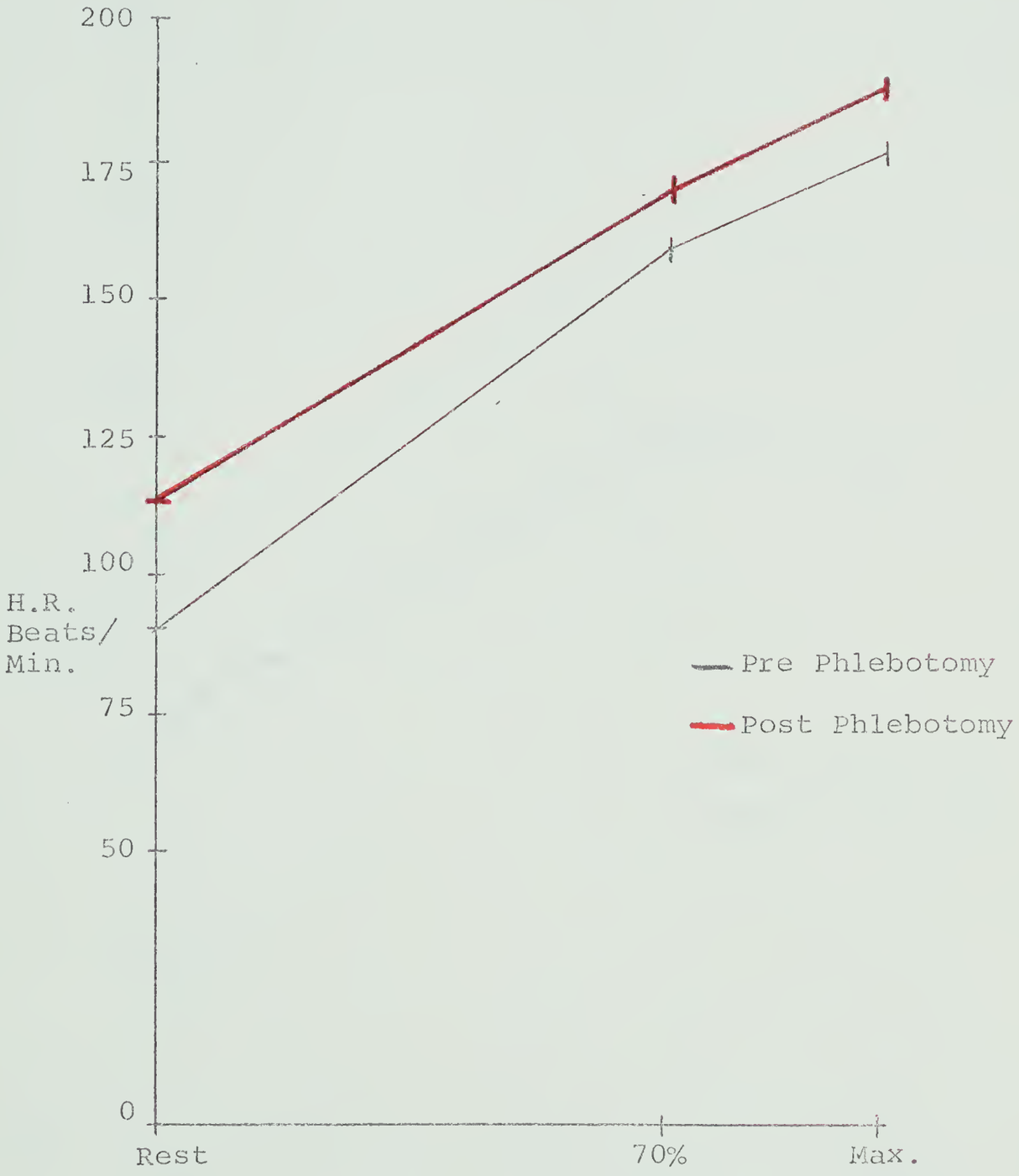


Figure 9

Relationship Between Stroke Volume and Worklevel

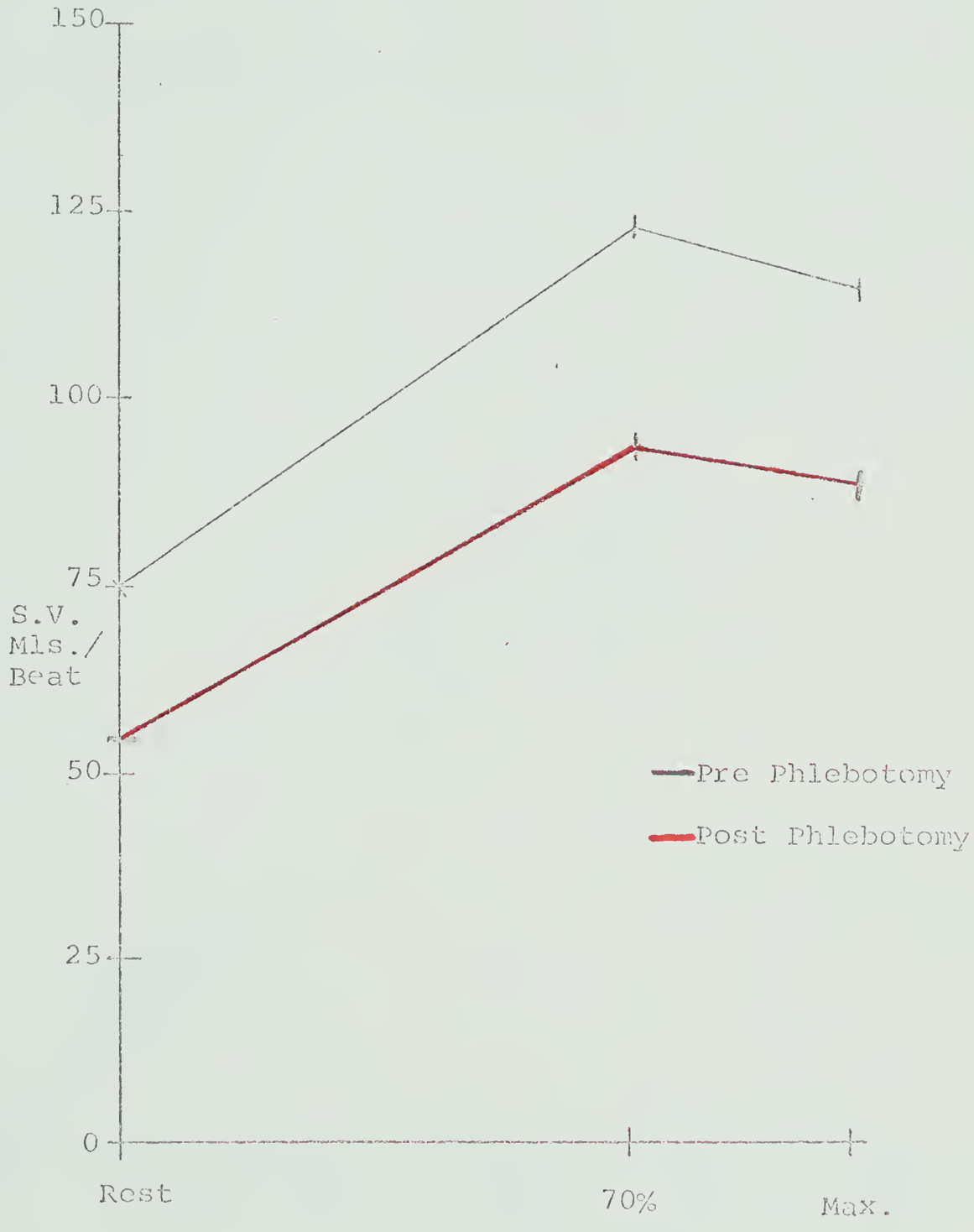
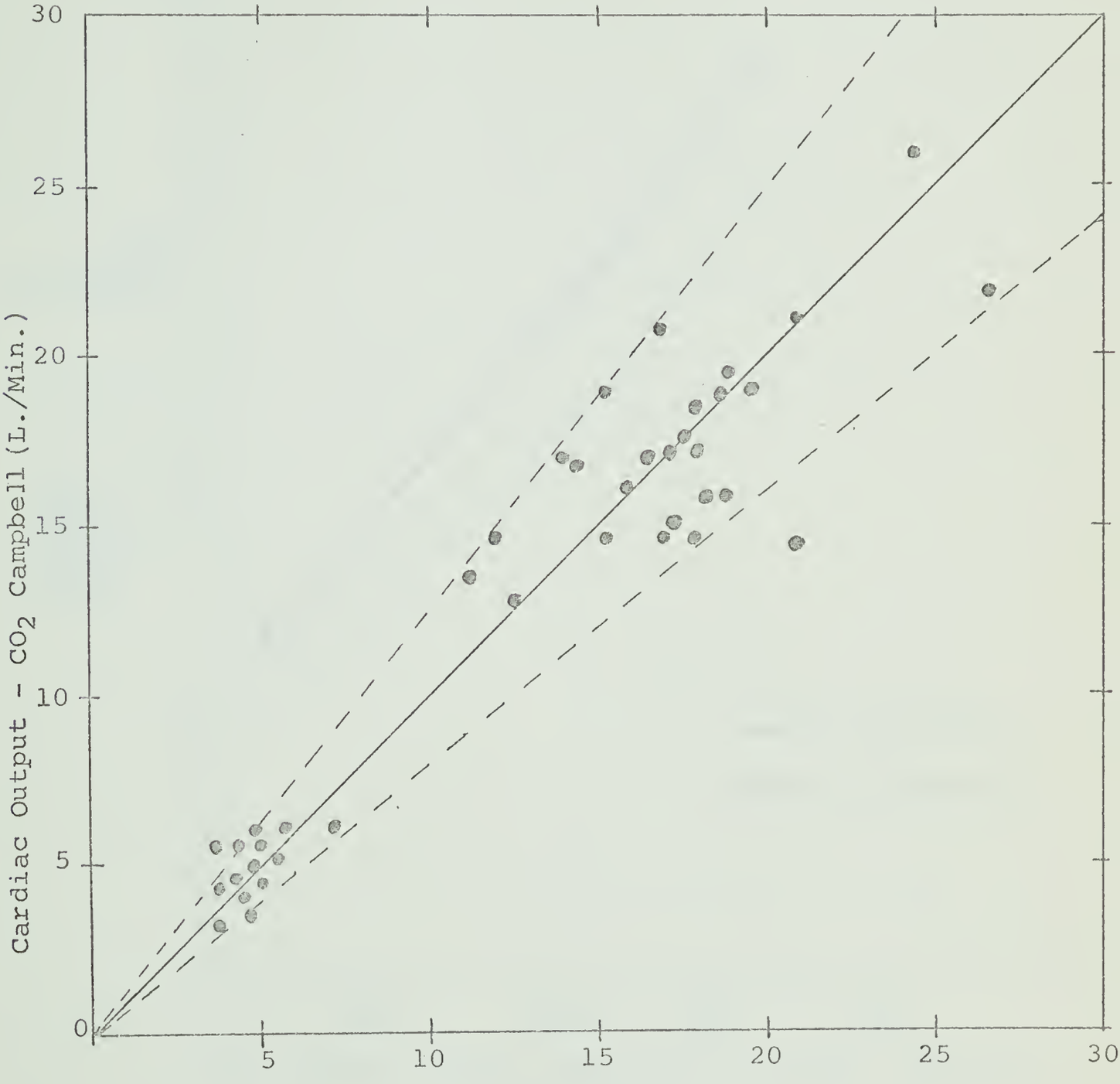


Figure 10

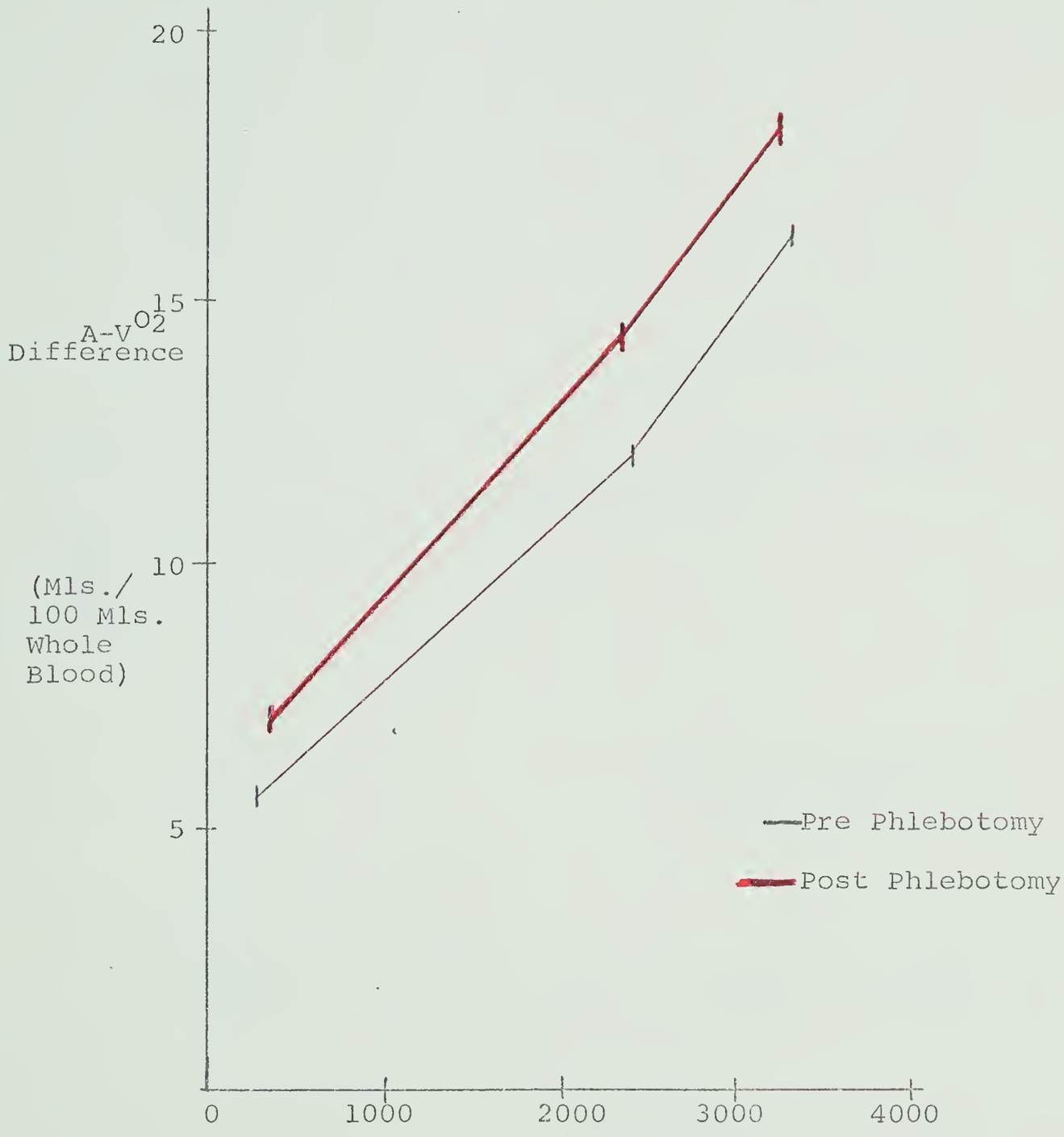
Relationship Between Cardiac Output Using Dye and Campbell CO_2 Method



Dotted Lines = $\pm$ 20% away from the line of identity.

Figure 11

Relationship Between Arterial - Venous Oxygen Difference and Oxygen Uptake



Mean Oxygen Uptakes (Mls./Min.) at Rest, 70% and Max. Ex.

Figure 12.

Relationship Between Arterial Oxygen Content and Workleval

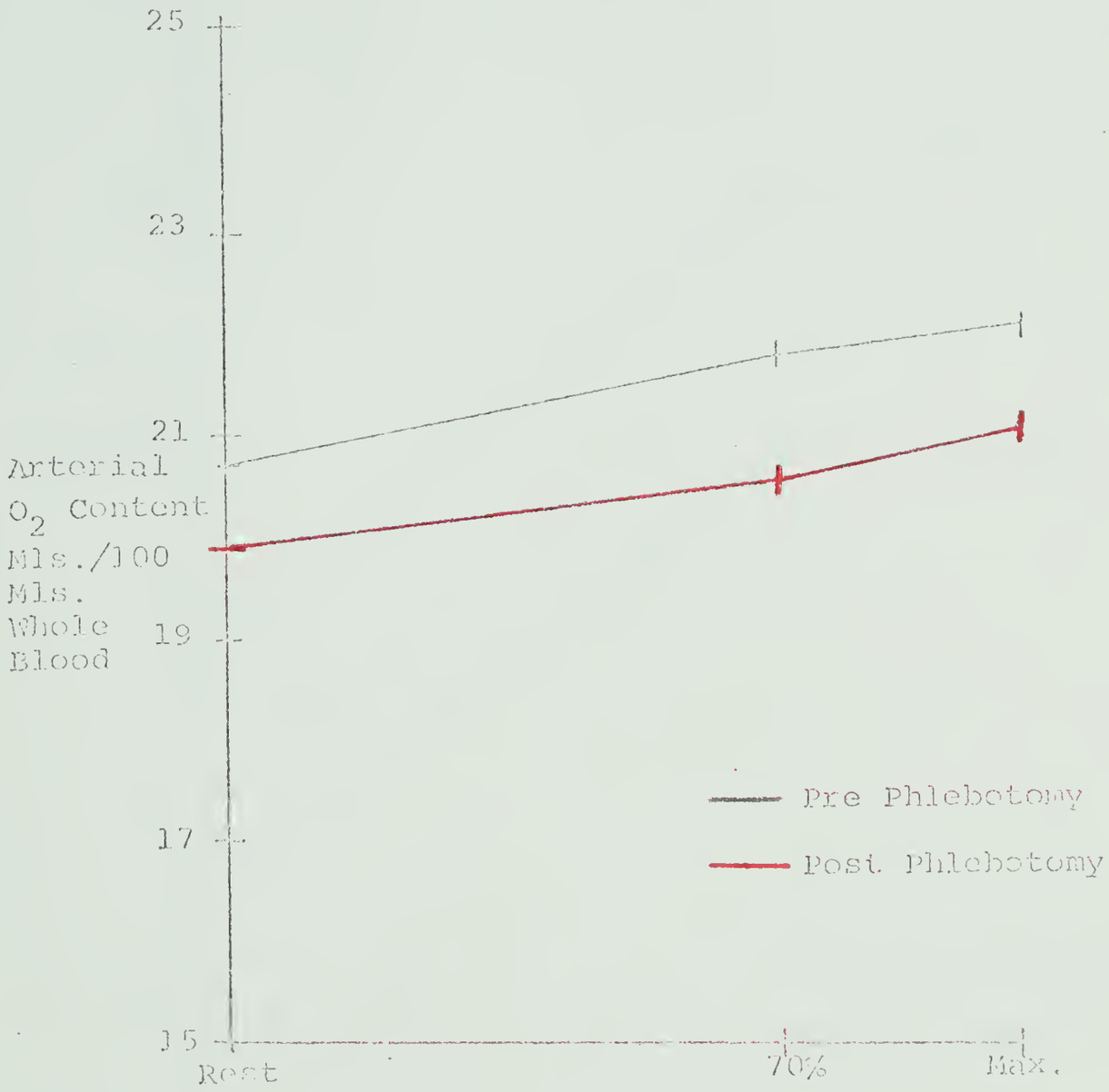


Figure 13

Relationship Between Mean Arterial Pressure and Worklevel

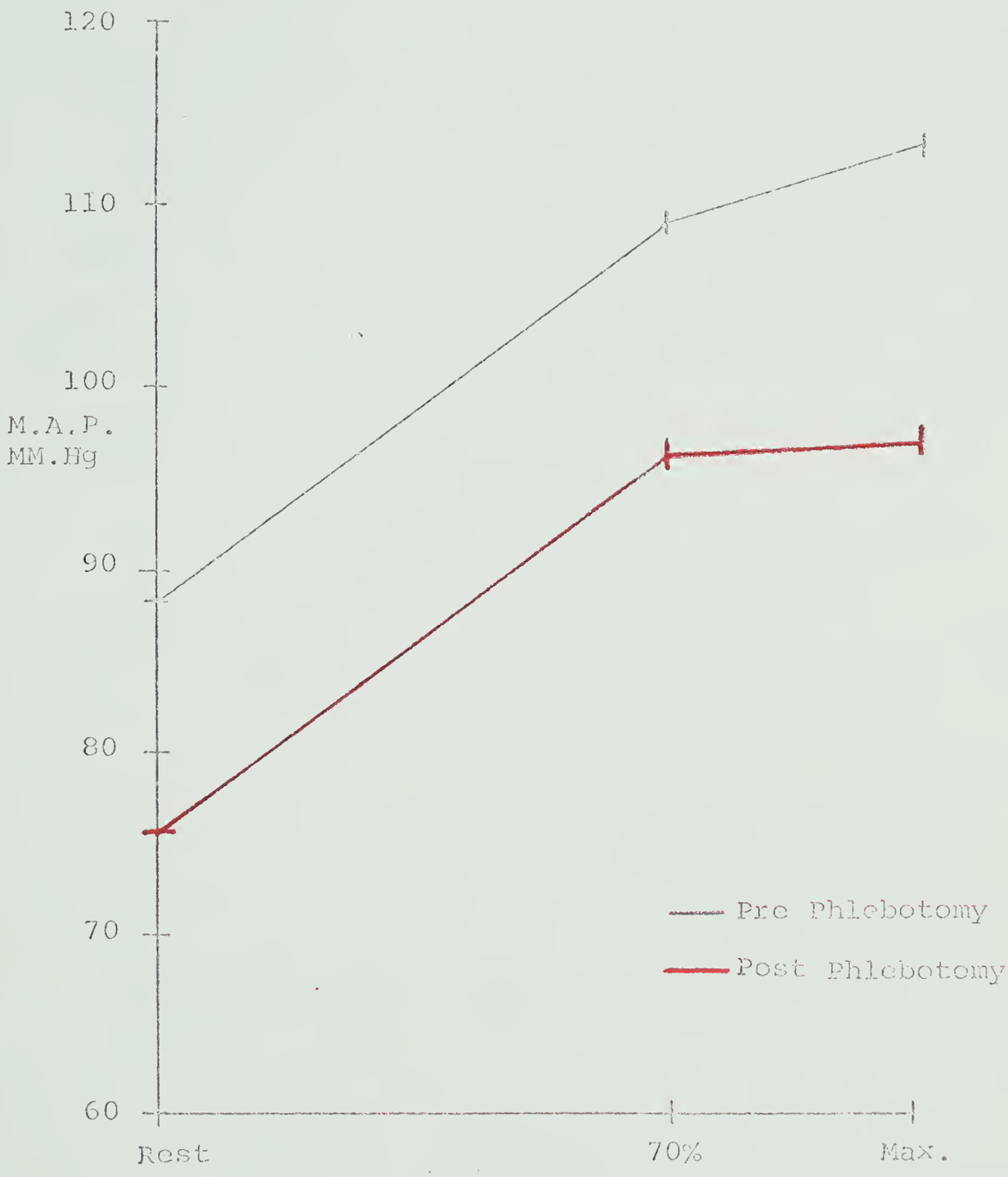


Figure 14

Relationship Between Central Blood Volume and Mean Cardiac Outputs

Figure 15

SUMMARY AND CONCLUSIONS

Oxygen uptake values in the post phlebotomy resting, submaximal and maximal exercise state did not change significantly nor did they change when tested again five days later. These subjects performed at an identical constant worklevel in pre and post investigations. For every liter of oxygen uptake utilized about 4.86 Kilocalories of energy are released, and a specific amount of energy is required for a respective amount of work. Assuming the muscular efficiency remains constant and the worklevel is constant, then the oxygen uptake theoretically should be equal. The oxygen uptake is also closely correlated with the mass of working muscle tissue and variations in working patterns could have resulted in minor variations of oxygen uptake values.

Cardiac output decreased substantially at rest and both worklevels in the post phlebotomy state. Heart rate increased very significantly but the concommitant significant drop in stroke volume was too great for the cardiac output to be maintained in upright positions. The reduction in blood volume of 10 ml/kg body weight (14 ml/kg including accessory blood loss) would result in strong sympathetic nervous stimulation and secretion of catecholamines from the adrenal medulla causing constriction mainly in the capacitance vessels and a decrease in vascular compliance. Total peripheral resistance was increased significantly at rest and non-significantly at exercise levels. Obviously, these compensatory mechanisms were unable to provide sufficient venous return to maintain cardiac output.

The CO_2 method of determining cardiac outputs proved to be reliable (r. 95 with dye curves) and reproducible at rest and all levels of exercise

on a bicycle ergometer. Although the method requires exacting measurements it is "bloodless" and convenient.

Finally, the MVO_2 was not significantly changed even though the post phlebotomy oxygen transport capacity was reduced. This maintenance of MVO_2, despite the reduced cardiac output, is mainly attributed to a translocation of blood to the working muscles and an increased efficiency of oxygen extraction which is not fully explained.

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APPENDIX A

GAS ANALYSIS COMPUTATION No. _____

Name _____ Weight _____ Kg.

Date _____

Temperature _____ o C.

Barometric Pressure _____ mmHg.

Bicycle Workload _____ Kpm. % of Max. VO_2 _____

Gas Collection Time _____ sec.

% O_{2E} = _____ x 2.5 = _____ %

% CO_{2E} = _____ %

% N_{2E} = 100 - (_____ % O_{2E} + _____ % CO_{2E}) = _____ %

Expired Gas Volume ATPS _____ L. + Analysis Vol. _____ = _____ L.

Conversion to Minute Volume ATPS = _____ L x 60 / _____ sec. = _____ L/min.

V_ESTPD = _____ (factor) x _____ L/min. = _____ L/min.

V_I STPD = _____ V_E STPD x _____ % N_{2E} = _____ L/min.

VO_2 Consumption = (_____ V_I STPD x .2093) = _____

-- (_____ V_E STPD x ._____ O_{2E}) = _____

+ _____ L/min.

VCO_2 Production = (_____ V_E STPD x ._____ CO_{2E}) = _____

-- (_____ V_I STPD x .0003) = _____

= _____ L/min.

VO_2 Consumption ml/Kg body weight = _____ ml. O_2 uptake =

_____ ml. Kg.

$$R.Q. = \frac{CO_2}{O_2} = \frac{\text{_____}}{\text{_____}} = \text{_____}$$

Appendix B

Cardiac Output (Campbell) Raw Data

Subj.	Work Level	$\dot{V}I$ S.T.P.D.	$\dot{V}CO_2$ L/min.	Pv_{co2}	Pa_{co2}
1. Pre	Rest	11.3	.280	49	35
	1100	61.0	2.75	77	42
	1600	98.0	4.12	77	32
Post	Rest	13.5	.27	44	26
	1100	68.5	2.57	79	35
	1600	105.0	3.40	71	28
2. Pre	Rest	16.1	.40	46	28
	1100	68.7	2.91	77	39
	1400	86.6	3.46	87	37
Post	Rest	14.2	.49	49	30
	1100	84.1	2.94	77	32
	1400	92.2	2.80	70	26
3. Pre	Rest	10.7	.34	52	38
	1100	63.9	2.55	80	42
	1500	98.7	3.45	91	35
Post	Rest	11.7	.29	50	35
	1100	88.3	3.53	86	33
	1500	103.6	3.37	84	34
4. Pre	Rest	14.2	.39	47	28
	900	72.0	2.50	77	39
	1200	80.9	3.04	91	39
Post	Rest	13.3	.40	46	34
	900	53.9	2.20	82	39
	1200	91.6	3.20	87	35

Appendix B

Subj.	Work Load	$\dot{V}I$ S.T.P.D.	$\dot{V}CO_2$ L/min.	Pv_{co2}	Pa_{co2}
5. Pre	Rest	11.6	.29	49	31
	900	56.0	1.96	63	31
	1200	96.4	2.65	66	28
Post	Rest	12.0	.30	49	28
	900	71.5	1.97	65	28
	1200	96.4	2.41	70	28
6. Pre	Rest	14.2	.43	49	31
	1200	72.0	2.88	82	39
	1800	107.0	4.30	105	42
Post	Rest	22.5	.45	49	32
	1200	76.4	3.25	86	39
	1800	107.0	3.96	105	35
7. Pre	Rest	12.3	.33	52	35
	900	67.5	2.70	77	38
	1200	75.0	2.80	87	38
Post	Rest	12.2	.30	47	31
	900	69.8	2.62	74	32
	1200	81.1	2.84	84	35

Subtract 1.4 + 2.6 ($\dot{V}CO_2$ mls.) from Pv_{co2}